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TREATMENT OF SURGICAL INFECTIONS BY CHEMICAL AND ANTIBIOTIC AGENTS

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SEROLOGY AND OBSTETRICS

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TREATMENT OF DIABETIC ACIDOSIS AND DIABETIC COMA

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Diagnostic Clinics

THIOURACIL, THIOBARBITAL, PROPYL THIOURACIL and the TREATMENT of HYPERTHYROIDISM

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DIFFERENTIAL DIAGNOSIS OF OBSTRUCTION AT THE BLADDER NECK

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International Assembly—St. Louis Auditorium, St. Louis, Mo., October 14 to 17 inclusive, 1947, 32nd year.

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Treatment of Surgical Infections by Chemical and Antibiotic Agents

FRANK L. MELENEY*

COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS, NEW YORK

In the last five years an overwhelming amount of literature has appeared on the subject of infections, particularly with respect to the chemotherapeutic and antibiotic agents.

Unquestionably in the last five years these newer agents have changed the whole aspect of infection, both medical and surgical. We have to get experience all over again on the behavior of infection under treatment with these new drugs. There is a temptation to use them promiscuously, and yet certainly if we are to improve our results we must use them with discrimination.

In reality, chemotherapy is older than medical history. This we know from the old papyri found in the ancient tombs of Egypt. We know that the same infectious diseases existed in those days that we see today, and we know from the prescriptions that were written that the doctors of those times used medicaments which we now call chemotherapeutic agents.

The antibiotics, however, open up an entirely new era, and we are just beginning to break the ground in that very fertile field.

With regard to chemotherapy, of which I should like to speak briefly at first, I wish to emphasize the point that back in the 1880's, when infectious diseases were definitely proved to be due to specific organisms, Koch, von Bering, Pasteur, and others studied the behavior and the nature of these organisms. At that time, the specific therapy of infectious diseases originated, but Koch and von Bering were par-

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The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University College of Physicians and Surgeons, and since January 1, 1946 under a contract between the Office of the Surgeon General, U. S. Army, and Columbia University.

Read before the meeting of the Interstate Postgraduate Medical Association of North America, Cleveland, Ohio, October 15 to 18, 1946.

Table I

SHOWING THE OVER-ALL RESULTS OF PENICILLIN TREATMENT IN SURGICAL INFECTIONS

	Results in Percentage					
	Favorable				Unfavorable	
Total Number of Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
744	14.8	49.9	64.7	17.8	17.6	35.4

ticularly discouraged in trying to find an agent which would kill bacteria without injuring the host. In fact, they predicted that it could not be done, but Ehrlich continued his researches and finally was rewarded, with the aid of Browning and others, by the discovery of salvarsan. But for the diseases caused by the lower bacteria, they found no agent which did not either damage the body or become inactivated by the tissues and fluids of the body.

Table II

SHOWING THE MOST FAVORABLE RESULTS OF PENICILLIN TREATMENT ACCORDING TO DIAGNOSIS

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
Furuncle	26	53.9	38.4	92.3	7.7	0	7.7
Cellulitis	36	64.0	27.7	91.7	8.3	0	8.3
Mastoiditis	6	0	83.3	83.3	0	16.7	16.7
Carbuncle	28	39.3	42.9	82.2	14.3	3.6	17.9
Suppurative arthritis	22	18.2	63.5	81.7	4.5	13.6	18.1
Lung abscess	11	0	81.7	81.7	0	18.3	18.3
Superficial abscess	32	25.0	56.3	81.3	6.3	12.5	18.8
Brain abscess	5	0	80.0	80.0	0	20.0	20.0
Osteomyelitis	153	8.5	68.0	76.5	13.7	9.8	23.5

Then came the dyes. Out of the great number of dyes tried, three gave encouraging results: gentian violet, acriflavine, and mercurochrome; but the damage which they did outweighed the benefit that they produced, and they fell into disrepute. A few research workers, however, continued the study of dyes, and out of it came Domagk's work and the demonstration that sulfanilamide, which was the active principle of his prontosil, could cure hemolytic streptococcus infections in animals. This was promptly followed by Colebrook's studies with puerperal fever, in which he clearly demonstrated that the mortality and morbidity of that common disease could be cut down by the clinical use of sulfanilamide.

I do not wish to go into the details, all of which I think are clearly in your minds, but I want to point out that the indiscriminate use of these agents without a knowledge of the bacterial causes in many cases followed this discovery. I am sure that you have heard doctors say, "I didn't know what the patient had so I gave him sulfanilamide." It was given for fevers of unknown origin with the hope that it would, and in many cases it did, control the infection. But results were disappointing in many cases and time was lost because the causative organism was not known.

ONE thing I want to emphasize is the necessity for a clear knowledge of the etiological agent, if it be possible, in any given case, so that the proper method and agent can be used in combating the infection. I will discuss that a little later.

The limitations of sulfanilamide, particularly in pneumococcus and staphylococcus infections, led to the development of derivatives which partially met those limitations. I think that we are all convinced from our experiences that sulfanilamide took the terror out of hemolytic streptococcus septicemia. In fact, in my own hospital in New York it practically disappeared from the wards, at least from the surgical side. Occasionally overwhelming hemolytic streptococcus septicemias would come into the medical wards, but we rarely saw them on the surgical side because the initial stages of the

disease were curtailed by the use of sulfanilamide and septicemia was prevented. But staphylococcus septicemia came along in just about the same frequency, and although it was hoped that sulfathiazole might meet that situation, it failed to do so.

The use of bacteriophage was of definite benefit in staphylococcal septicemia, but the difficulty of preparing a potent bacteriophage was so great that the commercial companies putting out bacteriophage without the necessary safeguards brought it into disrepute. It failed to measure up to expectations.

ment of Agriculture, the National Research Council, the Committee on Medical Research of the Office of Scientific Research and Development, with, of course, the help of those who came from England, led to its rapid production and made it available when our armies went across the Channel.

STILL the value of these chemotherapeutic and antibiotic agents during the war has come up for questioning, and I think the consensus is that we must give credit to the splendid organization of the medical department that

Table III

SHOWING THE INTERMEDIATE RESULTS OF PENICILLIN TREATMENT ACCORDING TO DIAGNOSIS

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Question-able	No Effect	Combined
Deep abscess	58	15.5	53.4	68.9	22.4	8.6	31.0
Thrombophlebitis	12	8.3	58.4	66.7	16.7	16.7	33.4
Sinusitis	6	0	66.7	66.7	0	33.3	33.3
Infected soft-part wound	37	13.5	51.3	64.8	21.6	13.5	35.1
Infected operative wound	70	5.7	55.6	61.3	21.4	17.2	38.6
Otitis media	7	28.6	28.6	57.2	14.3	28.6	42.9
Infected compound fracture	9	0	55.6	55.6	11.1	33.3	44.4
Ulcer of the skin	22	0	50.0	50.0	18.2	31.8	50.0

Table IV

SHOWING THE LEAST FAVORABLE RESULTS OF PENICILLIN TREATMENT ACCORDING TO DIAGNOSIS

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Question-able	No Effect	Combined
Empyema	54	0	47.0	47.0	26.5	26.5	53.0
Infected burn	31	3.2	42.0	45.2	29.0	25.8	54.8
Gas gangrene	9	11.1	33.3	44.4	33.3	22.2	55.5
Actinomycosis	7	0	42.9	42.9	28.6	28.6	57.2
Gangrene of skin	10	10.0	30.0	40.0	50.0	10.0	60.0
Miscellaneous	66	13.6	25.8	39.4	16.7	43.9	60.6
Postop. pneumonia	18	11.1	27.8	38.9	38.9	22.2	61.1
Peritoneal abscess	11	9.1	27.3	36.4	45.5	18.2	63.7
Diffuse peritonitis	18	5.5	22.2	27.7	22.2	50.0	72.2

When the war began, it was hoped that the sulfonamides (by that time sulfadiazine was available) would prevent or minimize the development of infection in war wounds, but it was the limitation of these drugs in these casualties, recognized first in England, that led to the further development of other agents, and revived interest in the antibiotic penicillin, which had been discovered some years before.

I think that we should recognize that the cooperative effort made in the development of penicillin was one of the great masterpieces of the supportive medical services of the war. The cooperation of the manufacturers, the Depart-

brought good surgeons up to the front line and effected rapid evacuation of the wounded, for the low mortality among the wounded in the war, rather than to the antibacterial agents, which must be regarded chiefly as adjuncts and secondary factors.

What I have just said applies particularly to the prophylaxis of infection, but we have, of course, the equally important problem of the treatment of established infection which I want to bring out in my next remarks. Let me point out first of all the difficulty of evaluating drugs or medical adjuncts in the treatment of surgical infections. We noticed in the early days of the

Table V
SHOWING THE RESULTS IN THE THREE GROUPS REPRESENTING THE LOCAL, GENERAL, AND COMBINED METHOD OF GIVING PENICILLIN

Method of Penicillin Administration	Total Cases	Results in Percentage: Favorable			Unfavorable		
		Excellent	Good	Combined	Questionable	No Effect	Combined
General, without local	438	16.7	44.7	61.4	20.0	18.5	38.5
Local, without general	142	16.2	54.2	70.4	15.5	14.1	29.6
Both general and local	164	8.5	59.8	68.3	13.4	18.3	31.7

sulfonamides that on the surgical services of the hospital, our results were not as favorable as those obtained on the medical side. We asked ourselves why that was so. It is obvious that surgical infections differ fundamentally from medical infections in several important respects. Surgical infections are distinguished by being amenable to surgery, that is, to an operative procedure. Obviously, the ideal treatment of infection is its complete eradication from the body, which can sometimes be obtained by complete excision. If that cannot be done without injuring the body permanently, an incision is used as a compromise. This carries away destroyed tissue and exudate, and permits an increased circulation to the part, thus aiding evacuation of the destroyed tissue by the body.

IN THE periphery of any surgical lesion where there has been a destruction of tissue or collection of purulent exudate, there are thrombosed blood vessels which prevent any agent in the blood from penetrating into the areas where the bacteria are most active. In medical infections there is a diffuse cellulitis which permits the blood vessels to carry in the medication. Where there is no destruction of tissue that agent can most effectively act upon the causative bacteria. Surgical infections in their initial stages are in that state, a diffuse cellulitis without a breakdown of tissue, and therefore, in the early stages these agents are much more likely to be effective.

There are certain conditions in which we know from experience that surgery has been absolutely necessary to cure the infection. Perhaps the best example of such a condition is acute osteomyelitis. It comes to us in the stage of septicemia in a very sick patient with high fever, often with chills, a positive blood culture, sometimes no local signs in any bone, but usually with some indication that the focus of infection is in the bone or near a joint. The roentgenogram does not reveal the destruction of tissue at first, but in the course of time there is a breakdown of bone which, in times past, has required a surgical procedure. Even so, cures were rare. If, in such a condition, the use of a drug will obviate the necessity for surgery, we must give credit to the drug for that accomplishment and for effecting a cure.

Furthermore, if the drug will permit a more limited type of surgery, as for example in many

Table VI
SHOWING THE RESULTS OF PENICILLIN TREATMENT ACCORDING TO THE PRINCIPAL BACTERIOLOGIC AGENTS ACTIVE IN SURGICAL INFECTIONS

Diagnosis	Total Cases	Results in Percentage: Favorable			Unfavorable		
		Excellent	Good	Combined	Questionable	No Effect	Combined
Hemolytic Streptococcus:							
Pure	16	12.5	56.2	68.7	12.5	18.8	31.3
Mixed	85	12.9	49.4	62.3	21.2	16.5	37.7
Coagulase-positive Staphylococcus:							
Pure	47	25.6	61.7	87.3	10.6	2.1	12.7
Mixed	98	10.2	55.2	65.4	23.4	11.2	34.6
Four principal gram-neg. rods:							
Pure	5	0	40.0	40.0	40.0	20.0	60.0
Mixed	95	1.1	49.5	50.6	25.2	24.2	49.4
Cl. welchii:							
Pure	1	0	100.0	100.0	0	0	0
Mixed	28	7.1	35.7	42.8	32.2	25.0	57.2

Table VII

GIVING A LIST OF PROBABLE CAUSES OF FAILURE OF THE 131 CASES IN WHICH PENICILLIN HAD NO EFFECT

1. The presence in mixed culture of organisms capable of producing penicillinase			58
Including:			
E. coli	22	*Aerobacter aerogenes*	8
Ps. pyocyanea	18	*Coli* intermediates	3
B. subtilis	18	Other gram-negative aerobic rods	5
B. proteus	15		
2. Tuberculosis			6
3. Tetanus			6
4. Penicillin-resistant staphylococcus			5
5. Penicillin-resistant streptococcus			2
6. Synergism (?) of hemolytic streptococcus and staphylococcus			9
7. Patient *in extremis* on admission			11
8. Too little			9
9. Too late			7
10. Too conservative surgery			9
11. Diabetes and arteriosclerosis			7
12. Metastatic brain abscess, hemiplegia or meningitis			5

cases of extensive ulceration, particularly the gangrenous types of ulceration; or if with the aid of a drug the natural duration of the infection is shortened, we must give some credit to the drug. That is often hard to determine in any given case, but we know in general the length of time certain surgical infections take. For instance, a carbuncle or a boil has its natural course both with and without surgical treatment. That is within the experience of all of us. If with the aid of a drug that time can be shortened, we must give the drug the credit for aiding in the treatment of that surgical infection.

In times past we have not thought it possible to close an abscess after opening it, but if with the aid of a drug, an infection can be excised or drained and then closed (it has been frequently done with osteomyelitis recently), we must give credit to the agent used in conjunction with the surgical procedure.

All of us who saw service in World War I had the experience of late secondary closure when the wound became clean and free from bacteria. With an undercutting of the edges, closure of the wound was possible and often resulted in prompt healing, but that procedure very often failed if hemolytic streptococci were present. Now if with the aid of a drug those secondary closures can be done earlier or with a greater incidence of success, we must give credit to the drug. Now, therefore, we have certain criteria by which we can determine when drugs are effective in surgical conditions.

There are definite limitations to the use of sulfonamides. There are the bacteriologic limitations, the lack of sensitivity of many organisms, the time limitation when a breakdown of tissue has taken place preventing the contact of the medication with the organisms, the limitation of the impenetrability of thrombosed blood vessels, and particularly the limitations of the so-called inhibitors. We know that broken-down tissue, exudate, pus, and so on, interfere with the local action of the sulfonamides, and probably constituted the chief factors during the war that prevented their favorable action in many cases.

THEN there is the limitation of toxicity, not only general toxicity, but the individual idiosyncrasy that sometimes produces very severe reactions. Last of all, there is the limitation of drug fastness when the organisms become resistant to the drug.

Penicillin, on the other hand, does not have many of these limitations. It is not only bacteriostatic, as the sulfonamides are, but it is actually bactericidal. It is not inhibited by broken-down tissue. It has a wider antibacterial range and is particularly active against the staphylococci. It has the same limitation of time, so that if treatment is delayed it is less effective. The chief inhibitors of the action of penicillin are the organisms which produce penicillinase. These organisms, chiefly of the gram-negative, aerobic rod groups, such as B. coli, proteus, pyocyaneus, and so on, completely

inactivate penicillin in many cases. I believe that the limitation of penicillin in war wounds was largely due to these associated organisms which are almost always present in such cases. That is particularly true in gas gangrene, in which there is almost invariably a mixture of organisms.

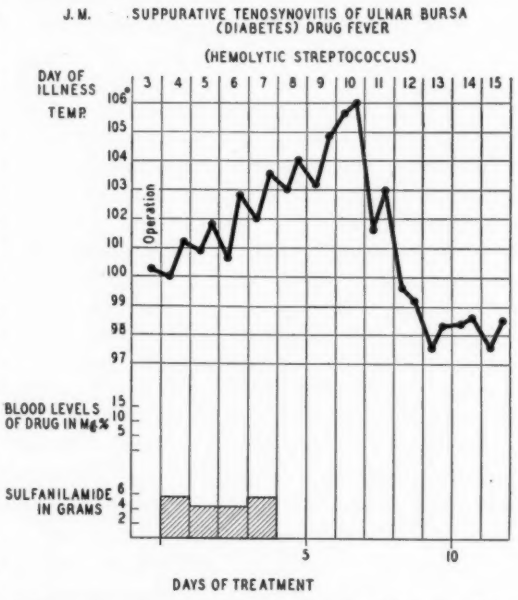
To sum up, I want to emphasize these things: These drugs are not panaceas. They have their limitations. There are definite indications for their use which should be recognized by all of us. It is absolutely essential at the present stage of our knowledge to learn as much as we can about the bacteriology of any given infection. If we haven't the facilities for determining the causative organism, we are greatly handicapped and our patients may suffer from delay in the proper treatment. Let me plead with you again to know the bacteriology before the treatment of any surgical infection and apply the agent or agents best suited to control the activity of every organism present.

I think it has been demonstrated beyond the shadow of a doubt that the sulfonamides have taken care of the great problem of hemolytic streptococcal infections. Furthermore, we can be pretty sure that penicillin has come in and taken care, to a large extent, of the staphylococcal infections. But there are still infections, particularly with mixed organisms, that are before us as problems to be solved. The antibiotic field has just opened up and we should pursue it with avidity, particularly to find agents which will inhibit organisms not controlled at present by the agents we already have.

Streptomycin is meeting certain types of infection, such as urinary tract infections, but its failure in a great many mixed infections is only too evident. Its great weakness seems to be the development of fastness by organisms which are not completely destroyed. The new antibiotic, bacitracin, with which we are now working, may be able to fill in some of the gaps left by the other antibiotics.

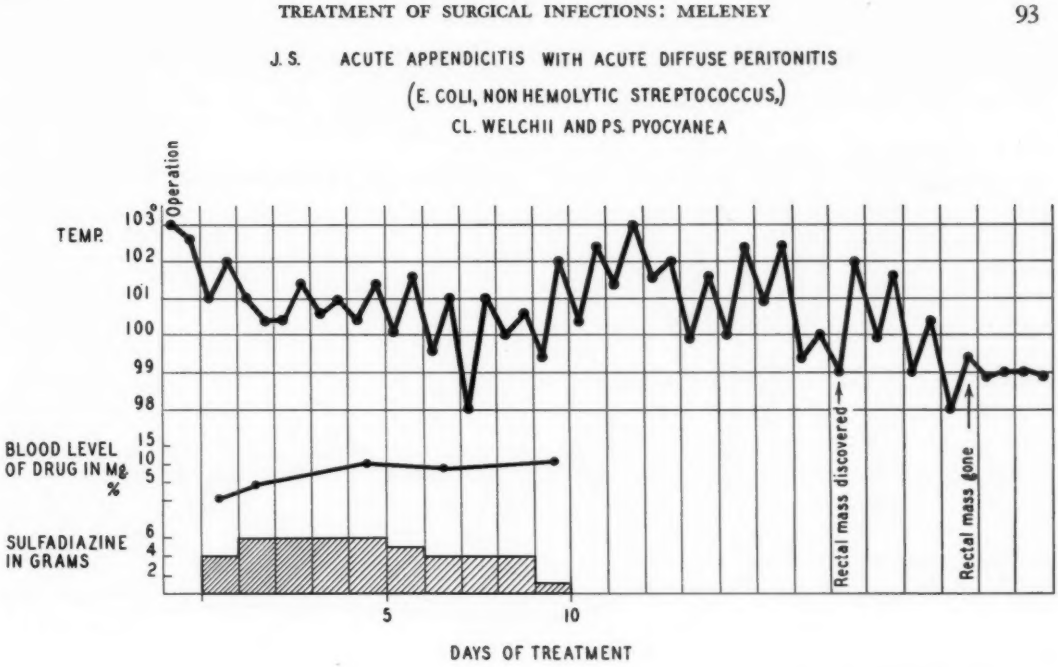
Some temperature curves illustrate more graphically than in any other way the results of treatment.

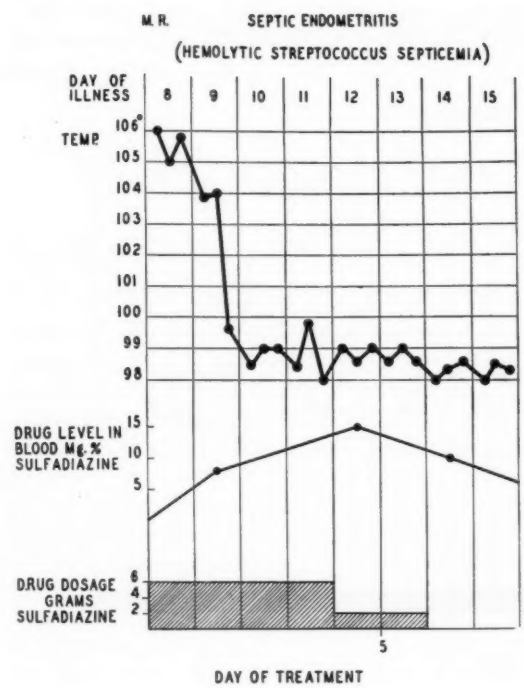
J. M. was a case of a tenosynovitis in the hand of a plumber who had the misfortune to puncture the distal margin of his ulnar bursa with a piece of wire. Infection was very rapid. It spread up through the ulnar bursa. We started treatment with sulfanilamide, but the progress of the infection caused us to proceed with the operation. We opened the ulnar bursa, and then continued with sulfanilamide. The local process rapidly subsided, more rapidly than it would have done without the aid of drug. However, his temperature continued to mount, and it was evident with the subsidence of the local process that he was developing drug fever. The drug was stopped, but still his temperature mounted. He had to be put into an oxygen tent to control his temperature and his restlessness. Then



his temperature came down and he made a rapid recovery. Here I think unquestionably the drug aided the surgical procedure in the cure of this man's hand and gave him a perfect result.

Note that this was a hemolytic streptococcus infection.





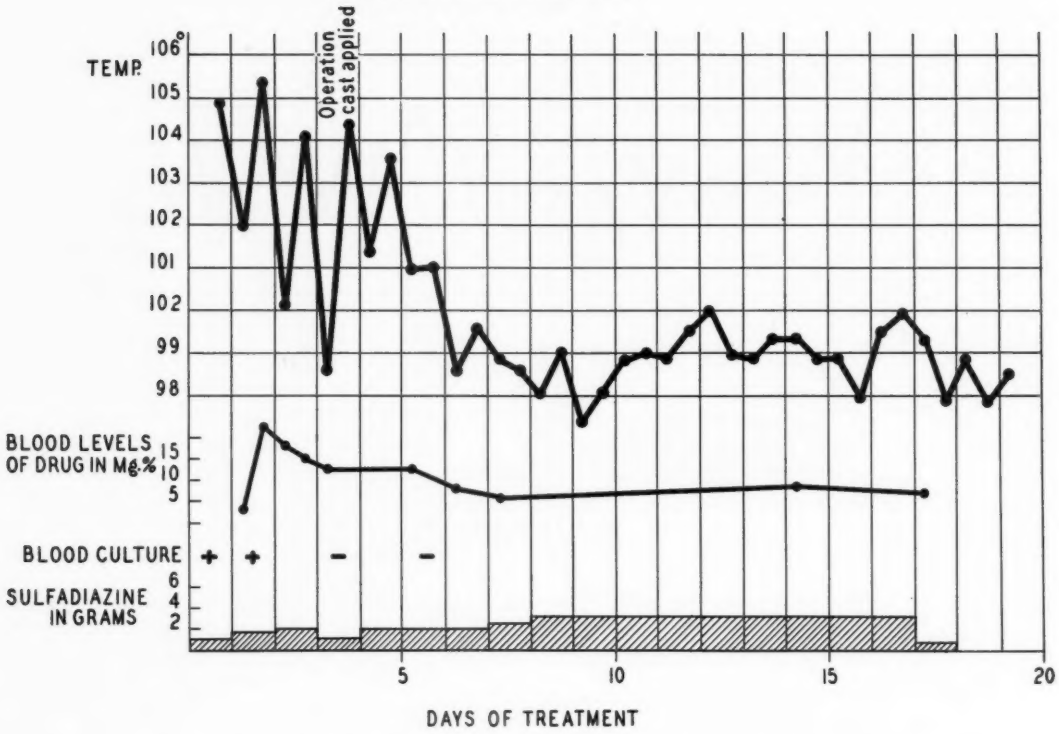
J. S. was a case of appendicitis where drug was given, with a fall in temperature but a secondary rise which we thought was drug fever. We stopped the drug and the temperature came down, then a rectal mass was felt. Without giving more drug that rectal mass disappeared. We had a resolution of a pelvic abscess without the use of drug, and we cannot be sure in this case whether or not the drug was effective in the early stages of the disease.

M. R. was a hemolytic streptococcus septic endometritis and it can be seen from the curve that there was a very rapid response to the drug. Again let me emphasize that this was a hemolytic streptococcus infection.

C. V. was osteomyelitis in a child due to a hemolytic streptococcus, with rapid resolution. In this case it was not certain whether the radius or ulna was involved. The radius was operated upon. No pus was found. Later roentgenograms showed that it was the ulna that was involved. In this case the operation was of no benefit, but there was a complete resolution and a regeneration of the bone without the aid of further surgery. A hemolytic

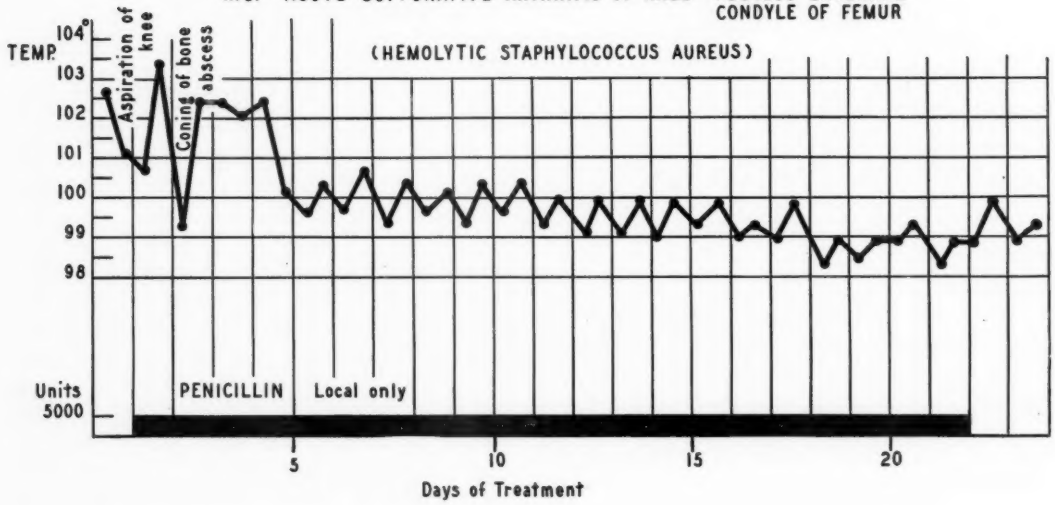
C.V. ACUTE HEMATOGENOUS OSTEOMYELITIS OF THE ULNA WITH SEPTICEMIA

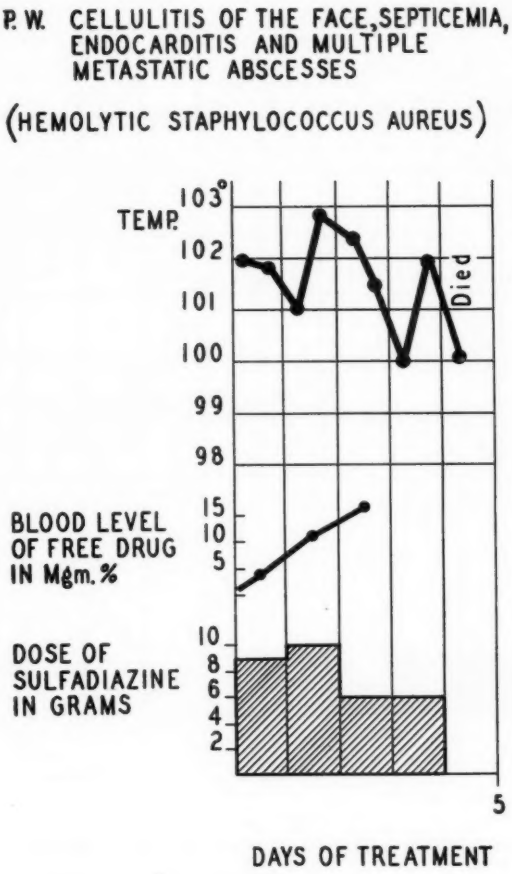
(HEMOLYTIC STREPTOCOCCUS)



W.D. ACUTE SUPPURATIVE ARTHRITIS OF KNEE - ABSCESS EXTERNAL CONDYLE OF FEMUR

(HEMOLYTIC STAPHYLOCOCCUS AUREUS)





streptococcus osteomyelitis, common in children, is rare in adults.

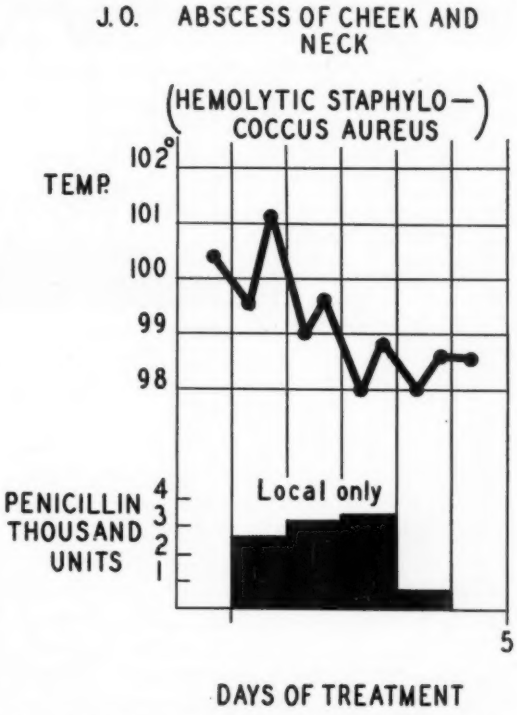
P. W. was a staphylococcus infection with septicemia in which sulfadiazine, in spite of a rising blood level, had no effect. At the autopsy an endocarditis was found, with multiple abscesses throughout the body. In this case the drug did not change the course of the disease, a staphylococcus infection. As a matter of fact, cures of staphylococcal infections with the sulfonamides were few and far between.

With respect to penicillin, I want particularly to point out that in surgical infections an opportunity is given for local treatment. In case J. O. an abscess of the face responded very promptly to local treatment, and surgery was obviated.

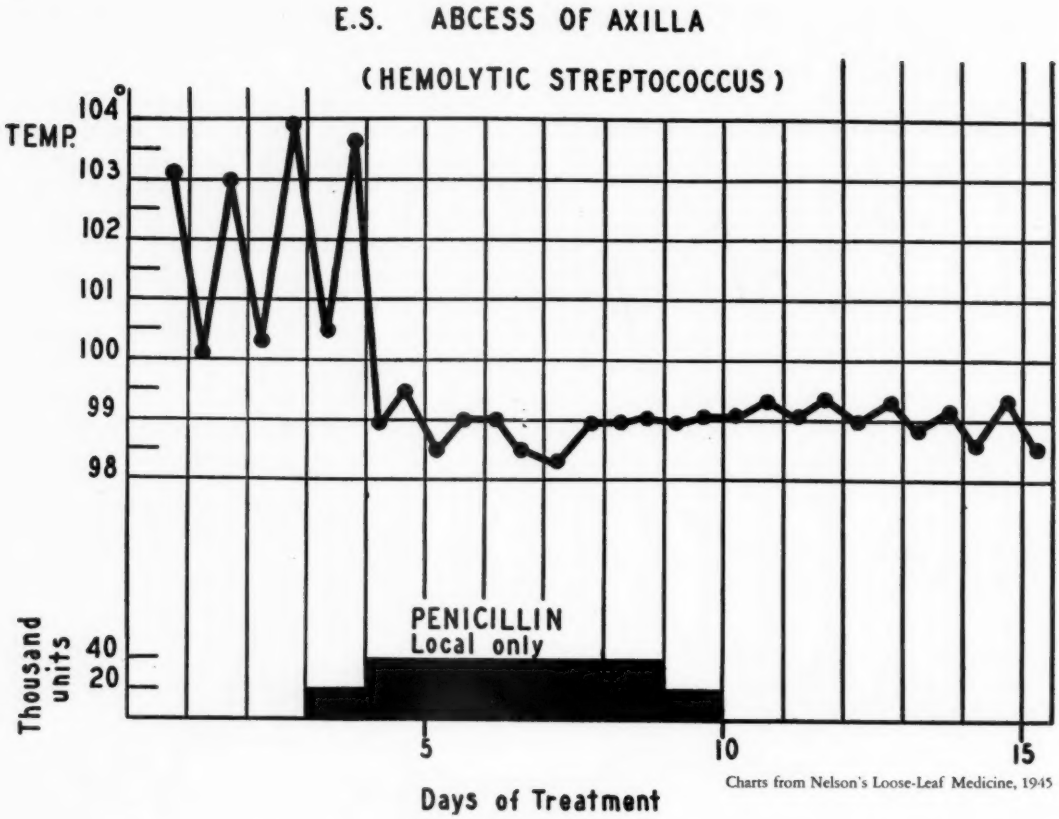
E. S. was a huge abscess of the axilla which responded to limited surgery and the local use of penicillin.

W. D. was a suppurative arthritis of the knee which responded after a single injection of 5000 units of penicillin. There was also a focus in the bone, which was later excised and treated only locally with penicillin. The cavity rapidly filled in with granulation tissue, permitting an early skin graft, and complete healing within 26 days.

I want to say just a word about our new antibiotic, bacitracin. In our study of contaminated civilian wounds we included soft part wounds,



burns, and compound fractures. Most of these were badly contaminated with organisms. We were hunting for evidences of antagonistic action in these bacterial mixtures. In one of the compound fractures we found a bacillus of the subtilis group which produces in the culture medium an antibiotic which is relatively nontoxic, and very active, with a wide antibacterial



Charts from Nelson's Loose-Leaf Medicine, 1945

range. For the last two years we have been using it locally in the treatment of surgical infections and we are now ready to consider systemic administration.

The table shows 65 cases which have been treated locally with this agent either in solution or in ointment form. We have divided the results as we have with a penicillin study into "excellent," "good," "questionable," and "no effect." The favorable response has been 84.3 per cent, the unfavorable 15.8, in a fairly wide range of localized surgical infections.

I feel the new field of antibiotic therapy has just opened up and will have a very important development in the next five or ten years, when search will be made for agents which will have specific action for the diseases not controlled by the agents now in our possession.

RESULTS IN 65 SURGICAL INFECTIONS TREATED LOCALLY WITH BACITRACIN

Diagnosis	Totals	Results: Excellent	Good	Questionable	No Effect
Deep abscesses	10	4	6	0	0
Superficial abscesses	7	2	5	0	0
Multiple abscesses of axilla	1	0	0	1	0
Furuncles	10	5	5	0	0
Multiple furuncles of face	2	0	0	2	0
Carbuncles	2	0	2	0	0
Infected sebaceous cysts	7	0	6	1	0
Infected operative wounds	4	0	4	0	0
Infected burns	1	0	1	0	0
Infected accidental wounds	1	1	0	0	0
Abscesses of chest wall	2	1	1	0	0
Ulcers in old scars	3	0	2	1	0
Impetigo	2	2	0	0	0
Styes	2	2	0	0	0
Synergistic gangrene	1	1	0	0	0
Miscellaneous	10	4	4	0	2
TOTALS	65	22	36	5	2
	%	33.9	55.4	7.7	3.1

Serology and Obstetrics

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OBSTETRICAL progress has become increasingly associated with serologic advance. This association began because of interest in blood transfusion, early envisaged as one of the most important obstetrical life-saving aids, continued in the quest of the causes of pregnancy toxemia, and culminated with the discovery of the Rh factor or substance and the relationship of maternal antitoxic substances to fetal injury and death. It now seems quite evident that blood incompatibility, certain pregnancy toxemias, and erythroblastosis fetalis and allied fetal cell injuries all stem from a toxin antitoxin mechanism.

This paper will confine itself to the cell substances, A, B, and Rh, which, among cell substances yet known, seem to be the most important in the causation of the above phenomena.

The argument maintains that the iso-agglutinins, demonstrable in human blood, represent, as in bacteriology, one of the functional arms of specific antitoxic substances, inherited or acquired: the other arms being the lytic and opsonic arms, again as in bacteriology.[2, 3, 19, 25]

When you mix incompatible bloods, the red cells of the blood containing the agglutinogen or agglutinogens are agglutinated by the specific agglutinin or agglutinins in the other blood, but the basic reason for the presence of the agglutinin or agglutinins lies in the fact that this blood comes from an individual whose cells are susceptible to the toxic action of the blood substances represented by the agglutinogens—the agglutinogens being but structural parts of these substances. The blood of a donor is incompatible with the blood of a recipient if it contains cell substances strongly toxic to the cells of the recipient and the blood of the recipient contains specific antitoxic substances, inherited or acquired.

The nearest approach to blood transfusion in nature may occur, at times and in infinitesimal quantities, between the fetus and its mother. If this occurs, and the fetal blood, due to the bisexual mechanics of human reproduction, and under the laws of heredity, contains one or more of the cell substances, A, B, or Rh, not possessed by that mother, and they can gain access to her cells, a toxin antitoxin battle ensues. If the mother is not adequately protected by a hereditary complement of specific antitoxic substances, or her cells are not vigorous enough to manufacture antitoxic substance actively, her organism may show characteristic signs and lesions grouped under the obstetrical caption of preeclamptic toxemia. If her antitoxic substances become too strong, they may in turn injure or destroy the fetal cells containing the toxic cell substances against which the antitoxin is specific, and thus injure or kill

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the fetus. The following of iso-agglutinin titers, both before and after delivery, in preeclamptic toxemia and in cases involving the erythroblastosis problem, has strongly supported this hypothesis.[13]

This obstetrical view permits a reasonable assumption in explanation of why, under the mechanism of heredity, and in our infinitesimal segment of time in human evolution, the group O mother inherits the anti-A and the anti-B agglutinins; the group A mother, the anti-B agglutinin; and the group B mother, the anti-A agglutinin. They contribute to her safety in the event that she bears a child whose cell substances are toxic to her cells, and these toxic cells and their circulating antigens can gain access to her blood. These agglutinins, arms of specific antitoxins, militate against her only in the event of gross transfusion of toxic blood. Gross transfusion of blood between individuals was not envisaged by nature.

In gross transfusion, and even in the intramuscular injection of blood, we should think in terms of toxic and nontoxic blood, as well as in terms of incompatible and compatible blood.[6, 20] Reactions to some intramuscular injections, and pathology found in some cases of delayed transfusion deaths, give glimpses of true toxic action. It is pathology similar in kind to preeclamptic pathology. In rapid transfusion deaths the effects of the toxin have not had time to manifest themselves, or they are entirely obscured by red-cell agglutination and red-cell detritus.

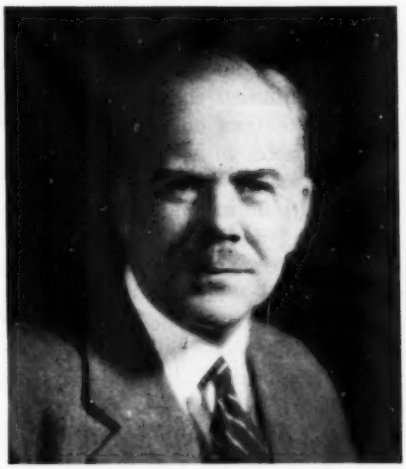
The following question immediately suggests itself: If this suggestion concerning the agglutinogen and agglutinin setups of the blood groups is correct, why is it that the Rh antitoxin is not inherited by the Rh-negative individual? The most logical answer, to date, would seem to be that the Rh substance has entered the species at a date too recent in evolutionary time to allow of its antitoxin becoming yet inheritable. If one will analyze the blood group setups from an ontogenic viewpoint, one will see that although the A and B substances, as shown by Kemp,[7] can be demonstrated in the fetus as early as the thirty-seventh day of gestation, the fetus' true complement of agglutinins or antitoxic substances does not appear until well after the two hundred and eightieth day.[22, 23] From this fact it would thus seem logical to argue that it takes in the neighborhood of eight times longer for an intraspecies specific antitoxic substance to become inheritable than it does for a cell substance to become inheritable.

IT HAS long been sensed by obstetricians that if toxemia of pregnancy is ever due to a fetal toxin—and clinical and pathologic data have increasingly pointed to this likelihood—the final proof would have to lie in the field of serology. For this reason every serologic lead has been followed attentively. In 1905, Dienst, due to similarities between pregnancy toxemia pathology and transfusion pathology, suggested that toxemia was caused by incompatible fetal blood gaining access to the mother. It can be seen in retrospect that this hypothesis failed of proof and was discredited because evidence was not then available that would allow the concept of the toxicity of the cell substances represented by the agglutinogens. The hypothesis was based on the concept of a static agglutinin, a mere hereditary characteristic, and was founded on the effect of agglutination of fetal blood upon the maternal organism.

It can be seen that in later serologic investigations of pregnancy toxemia, the therapeutic importance of gross blood transfusion has been so great, and the original definitions of the factors governing its safety or danger have been so adequate in this particular field, that our minds have been polarized, so to speak, and have been particularly obtuse in sensing the real nature of the factors involved. And again, even to this day, unless the mind is gradually accustomed to the light of new knowledge, the first reaction is to close the mind and oppose any change of viewpoint that would affect the original concept of the blood groups and their relationship to blood transfusion.

The idea of Dienst was resurrected in 1919, and pursued for many years, with the result that there was no generally accepted change in the previous conclusion that the theory of

fetal blood incompatibility as a cause of pregnancy toxemia was untenable. McQuarrie,[18] in 1923, reported that he found pregnancy toxemia sixteen and one-half times more frequent, where fetal blood was incompatible with that of the mother, than where it was not. It was felt, however, that these findings suffered from the error inherent in chance sampling, due to the unavailability of a large number of cases, because, under similar conditions, both before and after this publication, other investigators could find no significant difference between the number of group incompatible fetuses associated with the finding of toxemia in the mother, and the number not associated with toxemia. Again they could find no significant difference between the number of toxemics bearing group incompatible children and the number of toxemics in which fetal incompatibility could not be demonstrated. In the light of what was then known, an analysis of these findings could logically result only in a decision against the theory of fetal group incompatibility.



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If one reanalyzes the figures in the light of present knowledge, he realizes that, given any number of incompatible fetuses, and viewing the maternal protection that is afforded by fetuses that are not secretors, the protection of the placental barrier, and the protection afforded by a complement of inherited antitoxins, it would seem highly significant that 50 per cent of the mothers bearing these fetuses would develop toxemia. Furthermore it becomes significant that when only the A and B toxins are involved, they account for one half of the toxemias. If the Rh substance is added, the number of toxemias not demonstrably associated with a fetal toxin becomes smaller. As it has taken forty years to demonstrate an additional substance as important as the Rh substance, it is likely that other cell substances, important in disease, are still unknown. This assumption is rendered more likely by irregular crossmatching reactions not at present explainable. Today, it would seem that we are faced with the problem of how sure we can be that a toxemia, not showing a demonstrable fetal toxin origin, can be placed in the category of a toxemia due solely to cardio-vascular-renal inadequacy, either from heredity or disease. And, among the possible diseases, a previous toxemia must be included, and possibly antitoxin injury in fetal life.

The first data that led to a suspicion of the true character of the agglutinogens and agglutinins, and the substances they represented in blood were found in an article of Jonsson in 1936.[5] The data showed that if postpartum agglutinin titers were made on group O women, the anti-A agglutinin titers of women bearing group A children averaged higher than their anti-B agglutinin titers; and the anti-B agglutinin titers of women bearing group B children averaged higher than their anti-A agglutinin titers.

It seemed that these data might reasonably be interpreted as pointing to a functional reaction of an antitoxin in the mother to a toxin in the fetus. However, this interpretation was cast aside because it was not deemed to be within the canons of serology to associate a blood

group agglutinogen with a toxin or an inherited blood group agglutinin with an antitoxin. And besides, the fact that there was no significant increase in the number of toxemics showing an associated incompatibility with the fetus over the number showing no incompatibility, seemed to count out any involvement of elements associated with incompatibility.

As it still appeared increasingly evident from clinical observations that, in pregnancy toxemia, we were dealing with a fetal toxin, it was determined to approach the matter from a different serologic angle. To this end, a maternal intradermal skin test was devised, designed to show, in ways suggested by the Mantaux test, that whenever positive, it could be reasoned that a toxin was coming from the fetus and that the mother was immunized to this toxin.[12] The positive results of this test in toxemics seemed to raise the fetal toxin hypothesis to a high degree of probability, especially because they constituted forms of proof by prediction, a very strong form in the proof of a hypothesis. However, the work was soon given up because, even when positive, it failed to suggest the identity and nature of the toxin, and it could be taken only after the birth of the child. It was felt, however, that when negative, the test might be of diagnostic and prognostic value in placing the toxemia in the category of a toxemia arising wholly from a cardio-vascular-renal inadequacy, either due to heredity or disease.

THEN came the real illumination. It began with a report by Levine and Stetson in 1939,[15] of the iso-immunization of a mother by the fetus; continued with the discovery of the Rh factor by Landsteiner and Wiener,[8] and the demonstration, by Wiener and Peters,[24] of the danger of iso-immunization with the Rh factor in transfusion; and culminated in the work of Levine, Katzin, and Burnham,[16] Javert,[4] and others, showing the relationship of the Rh factor or substance to erythroblastosis fetalis and allied fetal injury. It was found, as experience increased, that the A and B substances could bring about a similar train of phenomena when the blood of the mother and fetus were similar from the Rh standpoint, thus showing that these substances could act similarly as toxins. It was found that, in about 30 per cent of the cases showing erythroblastotic phenomena, pregnancy toxemia was manifest.

Now when the light of this work was thrown upon toxemia, it was found that by titering maternal agglutinins both before and after delivery, one could predict, before delivery, the blood substances implicated if they were the A, B, or Rh substances, by the functional changes in the respective maternal agglutinins; one could recognize a functional relationship between the severity of the manifestations of toxemia and the titer of the agglutinin (antepartum, the lower the titer the more severe the manifestations tended to be; and, postpartum, the higher the rise of the titer, the more quickly the manifestations of toxemia tended to resolve).[13] In other words, we were witnessing a mechanism and train of phenomena paralleling those operating in snake venom poisoning or bacterial toxemia. It became apparent that the concept of the blood groups and blood group incompatibility had been dependent upon inherited antitoxic substances; the agglutinogens and so-called natural iso-agglutinin of the group being merely functional parts of a larger potential functional mechanism—a toxin antitoxin mechanism.

It would seem that the findings of Levine, Katzin, and Burnham can be interpreted only as an example of the quite generally accepted toxin antitoxin mechanism enunciated by Ehrlich. We are dealing with a functional toxin antitoxin mechanism and not with mere static blood characteristics that make it possible to differentiate types of individuals.

Assuming this to be a correct interpretation, it was predicted from analogy that one should be able to injure and kill a rattlesnake by the injection of rattlesnake antivenom. With the aid of Dr. W. J. Breckenridge, Director of the Museum of Natural History, of the University of Minnesota, this experiment was performed. Snakes of two sizes were killed, and slides of their normal vital organs prepared and read by Dr. W. R. Koucky, pathologist, Minneapolis.

Two snakes of corresponding age and size were then injected, each with 15 cc. of rattlesnake antivenom. In both snakes, within fifteen minutes, every muscle became clonically convulsed. The smaller snake, as would be expected, appeared to be the more seriously affected. In addition to the clonic contractions of its individual muscles, it assumed a perfect circular attitude, snapping convulsively at its vibrating rattles. It showed periods of apparent normality but died in eighteen hours. The cells of its vital organs showed suggestive signs of injury. The larger snake after several hours seemed to recover entirely, but it was killed in five days and the cells of its vital organs also showed suggestive signs of injury.

A snake, similar in size to the larger snake in the previous experiment, was given 15 cc. in divided doses of 1 cc. each every other day for a month. This snake showed no visible reaction, but the cells of its vital organs showed suggestive signs of injury. The term suggestive must be used pending thorough corroboration of abnormality and cause.

This work is being pursued to determine whether, after a long subjection to fractional dosage, a snake will eventually die, as is the case with the erythroblastotic infant, and show characteristic pathology. It is also hoped that it will throw some light on what is now suspected, namely, that though we may ostensibly clear up manifest pathology and save the lives of some erythroblastotic infants by blood transfusion, they may be handicapped by basic lesions of vital organs, basic lesions that cannot be cured. This basic injury may account for many abnormal conditions of each and every vital organ, conditions that we have previously attributed to hereditary causes.

It would seem that a host's immunization to snake venom differs from a mother's isoimmunization to a toxic fetus only in phylogeny. Both poisons come from cell substances. Lehrs and Putkonen, in 1930,[14] discovered that some humans secrete their A and B cell substances in their saliva, where it is found in higher concentration than obtains in the red blood cells. Some individuals do not secrete their cell substances. The former were called secretors by Schiff and Sasaki in 1932,[21] and it was found that 80 per cent of humans were secretors and 20 per cent were nonsecretors. The basis of this difference lies in the fact that in secretors the cell substances are in aqueous solution, whereas in nonsecretors the cell substances are in lipoid solution and can be extracted only with fat solvents. The hereditary character of these systems was established by Schiff and Sasaki. One may look upon it as a phylogenetic hangover. Thus, to a degree, secretors may be technically poisonous to certain other individuals. The peculiar appearance of some human bites corroborates the likelihood of this toxin antitoxin setup.

Snake venom is merely the concentrated saliva of the snake. That it comes from cell substances present in most, if not all, of the cells of the snake seems to be predictable from the action of each individual muscle cell of the snake when attacked by antitoxin. As one looks along the snake, reacting to antitoxin, the disorderly individual contractions of the muscle cells give the appearance of the surface of a lake ruffled by a slight breeze. At the same time the cells of the vital organs are injured. Thus the analogy between a toxic fetus and its mother and a poisonous snake and its host and the analogy between the reactions of the fetus and snake to antitoxin attack is not merely fantastic, but founded upon basic similarities that are more important than their dissimilarities, which, in logic, establishes the strength of an analogy.

Unless one distinctly visualizes the protective variants operating in behalf of the mother and in behalf of the child in the toxin antitoxin battle, one's average of perplexity over the correct interpretation of the absence or presence of disease manifestations, and over the actions of the agglutinin titers, will be increased.

The mother is protected by the relative larger bulk of her cells. This bulk operates to fractionate the dose of toxin to each cell. Again, no matter what the antitoxin generating power of each cell, the total amount of antitoxin developed is directly proportional to her bulk.

Upon the latter fact is based the estimation of the proper dosage of antivenom in snake poisoning. The dose has to be larger in children than in adults, not only because of the larger fractional dose of the toxin to each cell, but because the smaller bulk of cells of the child cannot afford sufficient additional aid by actively secreting antitoxin.

The mother receives the protection afforded by a normal placenta. And she is protected by inherited and acquired antitoxins. It is likely that she is protected to a certain extent if her fetus is a nonsecretor. But whatever the interactive protective or deleterious relationship between the secretor or nonsecretor properties of mother and fetus may be, can as yet only be conjectured. She seems free from any danger of antitoxin damage, because, as far as is known, whatever agglutinins are found in the fetus at birth come from the mother by filtration or some such method.[22, 23]

The fetus, it would seem, is relatively protected from maternal antitoxins by the fact, established by Kemp,[7] that fetal red blood cells are five times more resistant to agglutination than are adult cells. The same ratio may apply to the resistance of fetal red cells and fixed cells to the lytic or deleterious action of maternal toxins.

An important problem, which we know little about at present, is whether maternal toxic blood substances can reach the fetus and damage the fetal cells as fetal toxic blood substances tend to damage the maternal cells. This may account for many variations of fetal pathology. Clinical observations support this likelihood. To speak in traditional hematologic parlance, if maternal agglutinins can reach the fetus, and fetal agglutinogens can reach the mother, maternal agglutinogens should be able to reach the fetus. If so, it would seem that the fetal cells, unless especially resistant, as they are known to be to agglutination, should be easy prey. That they are likely to be especially resistant is evidenced by the number of apparently normal group O fetuses that are born to group A and group B mothers.

That the placenta acts to a certain extent as a barrier to maternal antitoxins is evidenced by the fact that though maternal agglutinins may be found in the fetus at birth, their titer is always lower than that found in the mother.[25]

In following antitoxin titers it is often baffling to have an agglutinin suddenly decrease in titer or even disappear. This phenomenon introduces another problematical variant, namely, the antibody absorptive power of the fetus. If the fetus be a secretor, all the fetal blood substances combined, in fixed cells, blood and all secretions and excretions, amniotic fluid included, may technically absorb huge amounts of antibody.

In regard to the toxemia problem and the toxin antitoxin setup, several observational sidelights are interesting. Theoretically the placenta is the front line of the toxin antitoxin battle. When one examines a placenta he is viewing the immediate remains of a possible toxin antitoxin battleground. It seems likely that many of the so-called infarcts mark leaks in the placenta that are filled with dead agglutinated attackers, the differences in coloration marking the progress of subsequent hemolysis. The gross and microscopic manifestations of placental aging and pathology have been comprehensively presented by Bartholomew and Kracke.[1] It would seem that the cause of some of these findings can best be explained from a toxin antitoxin viewpoint.

This process can be logically assumed to operate both for the weal and woe of mother and fetus. For the mother, it first tends to shut off toxic attack, but later under lysis results in the increase of liberated toxin. For the fetus, it first diminishes antitoxin attack, but tends to separate the fetus from its source of oxygen and sustenance,[10] and impedes its channels of elimination. The result may be premature delivery, before lethal or serious damage has been sustained by mother or child, or death and abortion of the fetus.

Infarcts are present in some degree in practically all placentae. Some of these infarcts may be due to mild toxic substances which are

known to be acted upon at times by agglutinins, inherited or acquired in other bloods, but apparently are little, if at all, implicated in toxemia. However, there has long seemed to be an increasing belief that widespread gross infarction correlates so highly with toxemia that it is likely an element in the cause of toxemia.[9, 11] If one follows anti-A, B, or Rh titers, he is more likely to come to the conclusion that a toxin antitoxin setup is the basic cause.

Antibody titer findings also seem to corroborate the clinical observation that general infections antedate and often precipitate toxemia by causing placental infarction, which infarction can be predicted and later computed as having occurred during the time of the infection.[9, 11] Infection as a cause of infarction has been called next to impossible by some, because bacteria and the usual signs of infection are not found around infarcts. Now, if one is following antitoxin titers, if a severe infection occurs, the titer strength of these antitoxins may be seen to rise to many times their previous level, and subside to their preinfection level when the infection resolves. It would seem highly probable, at least theoretically, that this rise of antitoxin strength would make infarction more widespread and conspicuous. If this be true, and the final necrosis of the infarcts increases the toxemia, it would seem justifiable to assume that the elimination of focal infection and the prevention of general infection would be indicated as prophylactic measures against toxemia. By the same token, this jump in antitoxin titer may be an added factor in accounting for the high correlation between infection and the death of the fetus and abortion, both by the direct action of the antitoxin on the cells of the fetus, and by placental infarction.

Since the work of James Young in 1914,[26] there has been a feeling that premature separation of the placenta and pregnancy toxemia have some causal relationship with each other. Attention to the blood toxin antitoxin setup makes it seem highly probable that they both stem from the same toxin antitoxin background, when they are related at all. One of the interesting features of this work is that you can test out the likelihood of toxin antitoxin background on your outstanding cases of toxemia and premature separation, from the beginning of your practice, if the dramatis personae are still available.

If one has made it a point to be present, if possible, whenever the abdomen has been opened, for any reason, in pregnancy toxemia or premature separation, he likely has concluded that the bizarre petechial and ecchymotic findings, unexplainable by anatomic analysis, can be accounted for only on a toxic basis. It is no exaggeration to say that, at times, the only clinical picture comparable to the pelvic findings can be found in the vicinity of snake bites.

It is a belief that the best approach to this whole matter is to insist on knowing the A, B, and Rh status of husband and wife as we insist on knowing the Wassermann status. It can all be accomplished with one drawing of blood and thus does not necessitate any additional inconvenience. It can be done very advantageously at the laboratory of the hospital chosen for confinement. It is inexpensive, and once obtained, need not be repeated in future pregnancies.

Far from producing unnecessary anxiety, experience proves that it has exactly the opposite effect. Popular articles and uninstructed social discussions have inspired an almost universal dread of the terrible Rh factor. This dread raises its head where you would least expect it. Invariably, both husband and wife express relief that consideration is being given to the blood condition, and they cooperate enthusiastically in having the tests made. No matter what the results of the tests, it gives one an opportunity of allaying inordinate fears and of convincing husband and wife alike of the infrequency of any disaster, because of nature's safeguards.

It gives the physician a feeling of reasoned preparedness. Its usefulness will be found to be infinitely more frequent than the Wassermann

knowledge, which of course is a prerequisite in proper care.

When, from principles of genetics, one can be quite sure that the infant cannot inherit an A, B, or Rh substance known to be potentially toxic to that mother, he can likewise be reasonably sure that he will not encounter pregnancy toxemia, premature separation of the placenta, or erythroblastosis due to a toxin antitoxin background. The likelihood of abortion is diminished, even if an acute infection occurs. Other setups can be marked "Watch" and extra care taken in their supervision.

One of the greatest advantages of this approach is that it permits the building up of sources of Rh-negative blood of every blood group that can be turned to, in case of need.

In an Rh-negative woman with an Rh-positive husband, especially if the slightest sign appears that can be attributed to a beginning toxemia, it is well to test, at regular monthly intervals, beginning at the sixth month, for the presence of an Rh antibody, if only to make preparations for the immediate examination of the infant's blood at birth and to line up appropriate donors if the antibody appears. One is often agreeably surprised to find a normal baby. Such experiences make it evident that, in general, one should not interfere obstetrically until one child has been born severely diseased. If you do, in the long run you will likely lose more normal babies from prematurity than you will save by intervention and immediate treatment, if this is found to be necessary. It is quite different after a history of one serious injury or disaster. Then, if in the next pregnancy the Rh antibody appears and rises, or the A or B antibodies are at fault and rise, one can be quite sure that he is dealing with another fetus of like toxic status, and, after one can be reasonably sure that the fetus has reached the age of viability, it would better be separated from the mother by Caesarean, or rupture of the membranes according to the presentation, position, station of head in the pelvis, and the condition of the cervix. The chance of success is much reduced below the normal low average of success, if what is known as a blocked antibody obtains. Where the latter obtains, most of these fetuses succumb before they reach the age of viability.

IF, FOR any reason, one does not like the all-out approach, above mentioned, an excellent and simple approach is to examine routinely the blood of newborns. Dr. W. R. Koucky, pathologist, has been doing this for five years at Abbott Hospital, Minneapolis. Any child with ten or more erythroblasts, to 100 leukocytes counted, and with a hemoglobin approaching 100, or below 100, is considered suspicious. The aim of this is not only to direct treatment, if necessary, but to call attention to the advisability of examining the blood status of husband and wife as a basis for future decisions. As erythroblastotic disaster very seldom appears in early pregnancies, and sometimes not even after iso-immunity has been demonstrated previously, this approach is excellent.

Some contend that there is no evidence that toxemia is caused by the Rh substance. A 30 per cent correlation would not seem to bear out this opinion. Furthermore, it is a belief, founded on clinical observation and titer studies, that many slight signs of toxemia are overlooked or not recorded, and that absence in 70 per cent of cases is due to a combination of overlooking slight signs and to the likelihood that the women in these instances are completely protected by the height of the antitoxin strength.

From the toxemia standpoint, the main importance of this whole argument is the direction that the findings give to the development of specific antitoxins to be used, in behalf of the mother, either after the intrapartum death of the child, or after the delivery of a live child, especially in antepartum and postpartum eclampsia. This direction is being followed.

In 1926, McMahon[17] published a preliminary report of the treatment of ten cases of preeclamptic toxemia, with astonishingly and conspicuously good results, by the administration of serum taken from a woman who was just recovering from a toxemia. His comments were, "We are unable to offer any satisfactory ex-

planation explaining these results, etc." He was not alone in not being able to prove the mechanism. But it did seem that if the results had any basis of cause and effect, it must be a toxin antitoxin basis. But what was the antitoxin and to what substance was it antitoxic? It was not suspected that the results had anything to do with the agglutinogens or the agglutinins, because by the canons, they were merely inherited properties or characteristics that permitted the division of humans into four groups, and had to do mostly with incompatibility and blood transfusion.

Well, McMahon's observations went by the boards just as had Dienst's theory of incompatibility, because with knowledge then at hand, the mechanism was not amenable to proof, and besides, it just did not always work. Present knowledge suggests that one could as reasonably, with any hope of success, give a woman suffering from an A substance toxemia, a B antitoxin; or a B and A antitoxin; or an Rh and A or B antitoxin, as he could give a person bitten by a snake whose venom is of the neurotoxic variety an antivenom operating against the hemotoxic variety.

Now, in closing, let us look at the obstetrical problems presented by transfusion.

It is true that by careful crossmatching, aided by Levine's incubational method and checked by serum suspension of red cells, transfusion can be made quite safe, even if the woman had been iso-immunized by a pregnancy or a transfusion by any known or unknown substance. However, what is considered of great importance by obstetricians, who have had any experience with erythroblastosis, is the danger of the future unnecessary increase of this disease if the Rh status of women is not considered before transfusion. It has been estimated that a transfusion is ten times more likely to iso-immunize a woman than is a pregnancy.

In the past few years, the frequency of transfusion in the proper interests of therapeusis, has increased tremendously. As yet, the indications for the proper use of transfusion in obstetrics have not reached the saturation point. But this very increase raises the apprehension that, unless more care is taken in giving only Rh-negative blood to Rh-negative women, except in extreme emergency, we are surely going to see a marked increase in erythroblastosis and allied fetal injury. Much of the obstetrical increase in transfusion is accounted for by the demands for transfusion in inevitable abortion in young women. There is no intent of exaggerating the danger that these young women may be iso-immunized with dire consequences to their future ability to bear healthy or viable children, but it does seem that this possibility should be continuously emphasized.

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The Treatment of Diabetic Acidosis and Diabetic Coma

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THERE is no one accepted technique for the treatment of diabetic acidosis and coma at present. Therefore, I can only discuss the method which I have used and with which I have had the greatest experience. It is not presented as the most perfect plan of treatment, but as a plan which has given satisfactory results.

DEFINITION

Diabetic acidosis—This is a clinical picture in which a patient with diabetes develops increased thirst, frequency, weakness, acetone breath, nausea, vomiting, abdominal and chest pains, soft eyeballs, and other evidences of dehydration; and air hunger (Kussmal breathing). The laboratory studies will reveal a glycosuria, ketonuria, hyperglycemia, leukocytosis, and a low carbon dioxide combining power. *However, the patient is conscious.*

Diabetic coma—When a patient with diabetic acidosis loses consciousness, *then, and only then,* is the diagnosis of diabetic coma made. Such a patient may be semiconscious—that is, he will respond to stimuli, but may be unable to take fluids or answer questions—or he may be unconscious so that he does not even respond to stimuli. I agree with Owens[1] that the term "diabetic coma" should be used only with those patients in ketosis, whose mental state has become one of unconsciousness. It is wholly a *clinical* diagnosis. True, the carbon dioxide combining power is usually low. This indicates only the degree of the acidosis, *not* the mental status of the patient.

DEVELOPMENT OF THE CLINICAL PICTURES AND THEIR MANAGEMENT

The mild case—Often a trained diabetic patient under observation will carry on, feel well, hold his weight, and be free from symptoms; though he has glycosuria, he will not show acetone in the urine. At times, during a slight upper respiratory infection, a gastro-intestinal upset, or an extreme sunburn, or even without apparent cause, the patient's thirst will increase, his urinary output will rise, and acetone will be found in the urine. The qualitative reading of the reaction may be 1 to 4 plus. Such a patient is not hospitalized. He is usually familiar with the tests for acetone and sugar and can follow his treatment at home. He is then told to follow these directions:

1. Test your specimens every time you void, for sugar and acetone.

2. If acetone is present, take regular insulin in amounts depending upon the quantity of sugar

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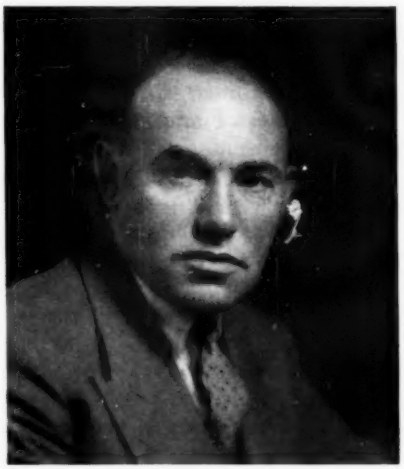

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found in the urine. That is, if the test is yellow, brown, or orange (4 plus) take 25 units; if the test is green with yellow sediment, take 15 units; if the urine is blue or free from sugar, take the juice of an orange.

3. Drink all you can—water, milk, fruit juices, ginger ale.

4. Take salty broths and if they are not available, two salt tablets (1.0 gm.—XV grs.) every two hours.

5. Continue this routine until three consecutive specimens are acetone-free. If acetone persists and you feel nauseous or vomit, come to the hospital at once.

By means of this home treatment the ketosis clears rapidly, and as the underlying cause improves, the patient can resume his former regimen. In cases where the ketosis appears without apparent cause, I have learned that an increase of the daily dose of insulin remedies the situation.

Case 1 refers to a typical clinical picture of acidosis.

Case 1

From 6:45 P. M. to 11:30 P. M. —25 units of insulin every half hour as specimens contained 4+ sugar and 4+acetone. WBC 25,800. Blood Sugar 425. CO_2—20 on admission. Patient received 1000 cc. 5 per cent glucose in saline at once and 7 doses of 50 cc. each of salty broth about 1 hour apart as well as about 1710 cc. of fruit juices. Water was given ad lib. Discharge Diet: P60 F60 C200.

Time, A. M.	Insulin Units	Sugar	Acetone	Diacetic Acid
12:00	25	4+	2+	0
12:30	25	4+	1+	0
1:00	25	3+	0	0
1:30	10	2+	0	0
2:30	0	1+	0	0
3:00	15	0	0	0
4:00	15	0	0	0
5:00	15	0	0	0
6:00	0	0	0	0
7:00	0	0	0	0
8:00	0	0	0	0

The moderately severe and the severe case—Before presenting a description of this group I want to state categorically that *every newly diagnosed* diabetic with ketosis, regardless of the severity of the case, should be hospitalized, chiefly because of the patient's lack of training. Because of hospital overcrowding, however, I have treated these cases at home. Here the help of a nurse or a member of the family was urgently needed. I taught them the routine of testing, left definite written instructions, kept in touch by telephone at hourly intervals, and made calls as often as I could. There were no dire consequences.

The moderately severe case developing ketoacidosis and coma may reveal the following pattern. The patient develops a sore throat or some other infection. His temperature rises, he develops malaise, and he has no desire for food. Since he has decided not to eat, he sees no necessity for taking insulin as he fears a reaction. He may not eat for one or two days or more, subsisting on fruit juices and other fluids and still reasoning that under these circumstances insulin is unnecessary. Soon he observes an increase in thirst and notes frequency. He then developes aching legs, weakness, restlessness, and, perhaps, some somnolence. He carries on. Soon there appear epigastric pain, nausea, and vomiting. His heart beats rapidly, and it becomes difficult for him to breathe. He or some member of the family becomes

alarmed, and either a physician is called or the patient is taken to the hospital. Often no medical aid is sought until the patient is unconscious or has been for many hours. When such a patient is admitted to the hospital, the infection will be treated by any of the modern chemotherapeutic agents. His diabetic acidosis or coma or both will be treated as follows:

1. If the patient is unconscious, insert a catheter into the bladder and clamp it. This will facilitate getting samples of urine for analysis.

2. Give 25 units of regular insulin subcutaneously every half hour until the clinical symptoms of ketosis begin to disappear and the urine becomes acetone-free.

3. If the patient can take and retain fluids, give 2 or 3 glassfuls (200 cc.) of fruit juice every half to one hour. Salty broths and other liquids are given as frequently as the patient desires.

4. If fluids cannot be given by mouth, give 1000 cc. 5 per cent glucose in saline at once, rapidly. The infusion is then continued at a slower rate until the oral route can be used. In any continuous intravenous therapy, great care must be exercised to prevent overloading the right heart. This hazard is present in the older diabetic with arteriosclerosis and the young cardiac.

5. After the urine has become free from acetone bodies continue giving 25 units of insulin and 2 glasses of orange juice every two hours for 4 or more doses.

Of 100 cases of diabetic acidosis and coma, so treated, there were 7 deaths of which only 2 were due to the acidosis per se, and of these 2, one was highly insulin-resistant.

Case II is that of a patient who had diabetes for 12 years.

KETO-ACIDOSIS DEVELOPS

FACTORS responsible for the development of diabetic acidosis and coma are (1) failure to take insulin, (2) infection, and (3) combination of the two foregoing factors.

In Joslin's experience "the commonest cause of diabetic acidosis continues to be laxity of treatment, consisting of dietary indiscretions or neglect to take an adequate amount of insulin, or both." These factors were the cause of 53 per cent of a group of cases; infection was accountable for only 23 per cent. In my

CASE II

Time	Insulin Units	BLOOD CO_2	BLOOD Sugar	URINE Sugar	URINE Acetone	URINE Diacetic	Therapy
8:00 A.M.	25	19	325	4+	4+	4+	1,000 cc. 10% gm. in Sal.
8:30 A.M.	25			4+	4+	4+	400 cc. water
9:00 A.M.	25			4+	4+	4+	200 cc. orange juice
9:30 A.M.	25			4+	4+	4+	500 cc. N/6 lactate
10:00 A.M.	25			4+	4+	2+	200 cc. water
10:30 A.M.	25			4+	4+	0	200 cc. water
11:00 A.M.	25			4+	4+	0	1,000 cc. 10% gm. in Sal.
11:30 A.M.	25			4+	4+	0	400 cc. water
12:00 A.M.	25			4+	4+	0	200 cc. water
12:30 P.M.	25			4+	4+	0	200 cc. orange juice
1:00 P.M.	25			4+	4+	0	200 cc. water
1:30 P.M.	25			4+	4+	0	400 cc. water
2:00 P.M.	25			4+	4+	0	1,000 cc. 10% gm. in Sal.
2:30 P.M.	25			4+	3+	0	100 cc. orange juice
3:00 P.M.	25			4+	3+	0	200 cc. water
3:30 P.M.	25			4+	2+	0	200 cc. water
4:00 P.M.	25			4+	±	0	100 cc. grape juice
5:00 P.M.	25			4+	0	0	500 cc. 10% gm. in Sal.
6:00 P.M.	25			4+	0	0	200 cc. water
7:00 P.M.	25						

Patient was taking R20-0-P25; was well until a month before admission when he began losing weight, along with polyuria and loss of appetite. He became nauseated three days before and did not take insulin. For two days before admission he vomited all food, became drowsy and when admitted vomited a small quantity of blood.

P.E. P120 R40 BP. 105/50 T37

Semi-stuporous, Kussmal, acetone in breath, eyeballs soft. Pharynx red. HBO 16: RBC 5.1: WBC 29,800: BUN 86. Acetone free in 9 hours.

experience infection and omission of insulin were the commonest causes for the precipitation of keto-acidosis and coma. The dietary breaks were not as impressive; after an analysis of 27 of our cases who did not adhere to a diet, we found that only 2 were eating more, while 25 ate less than their prescription called for. In a group of 220 cases of diabetic acidosis and coma, Bearwood and Rouse[2] state that only 9 can be listed as breaking diet.

Although there is a difference of opinion concerning the breaking of diet as a factor in the development of diabetic keto-acidosis, it can be categorically stated that the most important cause is the omission of insulin, or a relative insufficiency of it, since during an infection its efficacy is considerably reduced. Consequently, a quantity which may have been sufficient during health to maintain the urine free from ketones becomes inadequate during an infection, and ketosis ensues.

HOW KETO-ACIDOSIS DEVELOPS

At this point it is of interest to note how the diabetic develops keto-acidosis and coma. As you know, the overabundance of acetone bodies—acetone, diacetic, and betahydroxybutyric acids—in the blood and tissues causes an acidosis. This is brought about by a depletion of base. It was once thought that these acetone bodies were abnormal end products of fat metabolism. This hypothesis is not tenable today.

The experimental studies of many investigators have established the following facts. (1) Ketone bodies are normal intermediates of fatty acid catabolism in the liver—the only organ which manufactures them in significant quantities. (2) Ketone bodies so made in the liver are secreted into the blood stream where they are utilized by the peripheral tissues. This occurs both in normal and diabetic subjects whether or not insulin or carbohydrate is available. (3) Ketone bodies will not cause acidosis as long as their production does not exceed their utilization. However, when they are produced at a greater rate than they can be utilized by muscle and other tissues, they must of necessity accumulate; it is this accumulation—resulting from overproduction—in the blood and tissues that starts the vicious cycle of acidosis, depletion of base, dehydration, and coma.

Why does the liver overproduce these ketone bodies? The obvious reply is that the liver is using for its energy the substance from which these bodies are derived, namely, fatty acids. Stadie's[3] experimental studies led him to the conclusion that when the demand for fat calories exceeds about 2.5 gm. per kilogram per day, the production of ketones exceeds utilization, thereby producing ketonuria, and, if unchecked, leads to keto-acidosis and coma.

How can we prevent the liver from subsisting on fatty acids? By making carbohydrate available as liver glycogen. Liver glycogen has been termed the greatest factor of safety against ketogenesis. Here the hypothesis has been proposed by Mirsky,[4] and indeed supported by fine experimental evidence, that a decrease of liver glycogen is the most likely stimulus to ketone formation. This is quite logical, for as the available carbohydrate is lowered, the liver will metabolize protein and fat. And as the combustion of fat reaches the figure of 2.5 gm. per kilogram per day as postulated by Stadie, the production of ketones will be accelerated to a point surpassing utilization with a sequential ketosis.

If, therefore, the liver is offered carbohydrate (glycogen) instead of fat, will ketogenesis be decreased? Evidence answers this query rather conclusively. A rapid drop in ketonemia and ketonuria was observed by Mirsky[4] in depancreatized dogs after the administration of glucose intravenously. Root and Carpenter[5] also reported a drop in blood acetone from 70 to 44 mg. in a diabetic patient three hours after 50 gm. of glucose were given by vein. It is obvious that glucose alone can decrease acetone formation both in the diabetic animal and patient, but to supress ketogenesis insulin is also needed, since it has been shown that, when insulin is also used, the glycogen content of the diabetic liver increases more markedly[6], and that the glucose so stored is not as rapidly dissipated. Thus, the liver is offered carbohy-

drate rather than fat for its own metabolic needs.

From the foregoing it is obvious that the diabetic will develop ketosis and coma if the liver catabolizes fatty acids in abnormal quantities. The liver will do this if glycogen is not available for its energy requirements. And, in the diabetic, the reduced glycogen stores are further lowered by omission of insulin, infection, or any other condition which reduces the potency of insulin.

METHODS OF TREATMENT

EACH group that has developed and employed a technique for treating diabetic acidosis insists that all the steps of its particular treatment are based on sound physiologic grounds. Mortality statistics are produced to support the thesis that such treatment is most satisfactory and, as additional support, explanations are offered on why the death rate is higher elsewhere. Such comparative data are neither satisfactory nor valid because of the numerous factors which determine the prognosis in each case. It is generally agreed that the results are dependent on (1) the duration of unconsciousness, (2) the age of the patient, and (3) the presence of serious medical complications.

If similar cases could be treated by the various methods, the superiority of one method over another might be determined. However, such an ideally controlled clinical experiment is almost beyond hope. Owens[1] has stated that even the so-called "best therapy" in the unconscious diabetic is highly unsatisfactory, while the duration of acidosis without unconsciousness is of considerably less importance. All agree that for the best results early treatment is imperative.

The most frequently employed measures in the treatment of diabetic acidosis and coma are (1) insulin, (2) fluids and salt, (3) blood analysis, (4) glucose, and (5) adjuvants—that is, N/6 molar lactate, transfusions, alkalis, lavage, enemas, and stimulants.

Everyone agrees that insulin is most urgently needed, since diabetic acidosis and coma are the end results of a relative or absolute insulin insufficiency. Everyone, therefore, prescribes insulin—the difference is a quantitative one. The dosage recommended by various workers has varied from 25 to 400 units as the initial dose. Whenever the smaller doses are given, they are repeated at one-half hour to hourly intervals until improvement, as judged by clinical and laboratory data, is apparent. Olmstead[7] gives 100 units at once and if there is no drop in the blood sugar after one and one-half hours, another 100 units is given. Joslin's group of 141 cases received an average of 206 units during the first three hours. There are still other variations, and the fact that good to excellent results have been obtained by all methods suggests that insulin is important, but that one dose or its frequency of administration is not superior to another dose given more or less frequently.

We have given 25 units—a small dose—at frequent intervals of 30 minutes. This plan, though empirical, has been satisfactory. That does not mean that giving 50, 75, or 100 units is not good therapy, even though the outcome in a series of cases may be poor. Owens[1] used 50 units of insulin every half hour at the start, and then altered the dose as indicated by progress. He also used all adjuvants, but reports a high mortality. Of 92 patients admitted, 49 were unconscious with an average of sixteen hours of coma. Among this group of 49 there was a death rate of 73.5 per cent. Does that mean that Owens's technique is inferior to ours, or that some one bungled the therapy? Not at all. His work is done in a general hospital with an active ambulance service, and he is called upon to treat more severe and more neglected cases than we do.

I decry the statement that some one has blundered if death occurs as a result of diabetic acidosis or coma. Many cases die in spite of generally accepted "superior" therapy, and no satisfactory explanation can be offered as to why death occurred. Schecter, Weisel, and Cohn[8] suggest that peripheral vascular failure causes such deaths. Danowski, Winkler, and Peters[9] state that the profound loss of salt and water may be the causal factors of such failure.

These hypotheses may be tenable as the patient in ketosis with shock has a decreased blood volume, a hemoconcentration, a hypochloremia, and a falling blood pressure. That may be the picture terminally. However, I have observed comatose diabetics whose blood pressure was maintained, whose chemical picture was corrected, and in whom no clinical evidence of peripheral failure was apparent. The therapy was considered adequate and yet such patients never regained consciousness.

The use of salt and fluids to replace the loss of base and water is so universal that no comment is needed. Often sixth-molar lactate was also used and transfusions were given only as indicated. We do not rely upon either the level of the blood sugar or the carbon dioxide combining power as guides of treatment. In our hospital and probably in others the results of the blood examination may not be available for one to three hours, at which time the data are of academic interest. Our principal laboratory guide is the examination of the urine for sugar and acetone at one-half hourly intervals, and we continue the insulin dosage of 25 units as long as acetone is present. The test is reliable and rapid, and therefore very practical.

THE question of whether or not glucose should be used in treatment of diabetic acidosis and coma has been argued with much passion and emotion. Many statements concerning the deleterious effects of glucose have been based on circumstances that were merely fortuitous. Our experience with glucose has not been unfavorable. As I have indicated above we have used it as a 5 per cent and occasionally a 10 per cent solution intravenously. The median given in a twenty-four hour period was 112 gm. When the amount given by mouth was added to that, the median amount rose to a total of 312 gm. for the first 24 hours, with a minimum of 50 gm. and a maximum of 800 gm.[10]

Now it has been stated by Root[11] and his associates[12] that glucose in doses of 50 or more grams is harmful because (1) it obscures the actual blood sugar values thus eliminating a guide for insulin dosage; (2) it may produce liver damage; (3) it neutralizes the action of insulin; (4) the hyperglycemia thus produced is harmful to the pancreas; and (5) it may provoke anuria. It is also stated that such large doses are not necessary since the body can only metabolize 5 to 10 gm. per hour. These statements are made by respected leaders in the field with such conviction that the physician whose opportunity to treat diabetic acidosis is limited accepts them as facts. It is desirable to appraise them and see what evidence is available to support them.

That the administration of glucose obscures the actual blood sugar is a *fact*, and I have no objection if one wishes to use the blood sugar as a therapeutic guide. I maintain, however, that it is the excessive ketonemia, not the hyperglycemia, that is the underlying cause of diabetic acidosis and coma, and that therefore the ketone bodies in the urine are more accurate guides of therapy. Insulin should be continued frequently until the ketone bodies

TABLE A

Date	Fluid Intake	Urine Output	Glucose Gm./24 Hrs.	Urea N.	BLOOD Sugar	BLOOD CO_2	BLOOD Chlorides	Serum P.	Icteric Index
2/11	6350	170	870	65	223	62	479	4.4	—
2/12	2700	73	490	65	133	60	469	5.3	5
2/13	3795	21	760	69	190	49	446	5.5	—
2/14	2360	30	300	73	85	57	429	5.3	11
2/15	3930	47	700	85	89	51	423	5.1	—
2/16	3900	37	400	—	—	—	—	—	—
2/17	2800	105	300	—	—	—	—	—	—
2/18	4970	108	425	89	77	45	399	4.8	5
2/19	3815	908	400	100	79	41	376	—	—
2/20	3885	1930	300	104	—	40	385	5.0	—
2/21	4330	3150	500	111	85	40	396	5.1	—
2/22	4200	3850	500	102	—	45	421	—	—
2/23	0	4200	400	96	—	37	424	5.4	—

vanish; then there is no problem if one wishes to treat the hyperglycemia.

Astwood, Flynn, and Krayer[13] have shown that liver damage occurred in dogs receiving glucose by vein at the rate exceeding 40 gm. per square meter per hour. They also demonstrated that dogs tolerated indefinitely 12 gm. per square meter per hour. These experiments have been offered as evidence that glucose may produce liver damage. Such reasoning is fallacious. Excessive quantities of any innocuous agent, even water, will prove toxic, and the fact that a dog may not be able to tolerate large quantities of glucose does not necessarily indicate that man cannot.

Recently, we had an opportunity to observe a patient in whom large quantities of glucose were not hepatotoxic. Following transfusion, a young woman developed a kidney shutdown. To facilitate diuresis large quantities of glucose were given by vein. Data are shown in Table A. This patient received from 300 to 870 gm. of glucose daily by vein. There was no glycosuria. Most of her blood sugars were normal, and one is led to the conclusion that the glucose so given was metabolized at a rate of 12.5 to 36 gm. per hour. Histologically, the liver showed no abnormalities.

Rabinowitch, Fowler, and Bensley[14] have shown that the diabetic with the aid of insulin can also utilize more than 5 to 10 gm. of glucose per hour, as illustrated in Table B which follows:

TABLE B

Hours	32	48	43
Glucose Intake	1020	780	835
Excreted	10	32	63
Utilized	1010	748	772
Gm./Hour	31.5	15.5	18.0

It is true that Root and Carpenter[5] used a different approach in determining how much glucose was metabolized. However, other data as well as ours are clear. It is obvious that if in my patient the glucose was not excreted it must have been used by the body.

The "neutralization" of the insulin by glucose is questionable. Perhaps, that is not what was meant, but the choice of the word "neutralize" was not the most desirable one. The interaction of insulin and glucose is not the same as the neutralization of an acid by an alkali. Insulin favors the accumulation of glycogen, but its mode of action is not yet understood. Its action has been compared to an enzyme substrate reaction; and whether or not an excess of glucose is present, a certain amount will be acted upon by the quantity of insulin available. The beneficial effect of the insulin is not nullified by the excessive amounts of glucose.

Insofar as excessive quantities of glucose being harmful to the pancreas in the treatment of diabetic acidosis and coma, that is highly speculative. My own observations on postmortem material failed to reveal histological changes in the pancreas in many instances. This is not an unusual observation, as Root also quotes two fatal cases which were treated with glucose in addition to insulin and whose blood sugars were 475 and 667 mg. per cent, and yet the autopsies were negative. It seems to me that there is altogether too much condemnation of glucose in the treatment of diabetic acidosis and coma. This indictment is not based on sound evidence.

I doubt whether the use or non-use of glucose is the crucial issue. I am sure that "suitable" cases will recover both with and without the use of glucose as long as adequate doses of *insulin, salt, and fluids are used*. The patient who has had a long period of unconsciousness will probably die in spite of the so-called "very best" treatment. Personally, I have had good results with frequent small doses of insulin and the use of glucose. The addition of glucose gives me the added feeling of security that I will not throw my patients into the hypoglycemia phase thus putting an additional burden upon a circulatory system already under considerable stress.

SUMMARY

1. Patients with diabetic acidosis, diabetic coma, or both can be successfully treated by giving small and frequently repeated doses of regular insulin—25 units every half hour—by replacement of water, and by giving salt and glucose by mouth, vein, or both.

2. The administration of glucose by vein or orally is beneficial and not harmful. Data are presented to support this thesis.

3. It is unnecessary to follow the blood sugar or the carbon dioxide combining power as guides of therapy. Our experience has shown that the clinical response and the disappearance of the ketone bodies are excellent guides.

4. The earlier the treatment is begun, the more favorable is the prognosis. Exclusive of medical complications, it can be stated categorically that the longer the patient remains unconscious, the less favorable are his chances for recovery.

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MONGOLISM

The diagnosis of mongolism not infrequently is made by parents who after a long period of emotional attachment realize that their child is not "right." Cummins and Platou point out that this brutal accident may be avoided if the physician has better knowledge of the stigmata associated with this deformity. These investigators selected three characteristics which occurred most consistently in known mongoloid idiots and compared the diagnosis, using these criteria with those obtained clinically. The criteria are: (1) a distinctly transverse alignment of skin ridges in the distal region of the palm; (2) a patterning of ridges in the hypothenar area, forming an arch, whorl, or loop; and (3) a triradiate arrangement of ridges at or near the center of the palm. The two latter characteristics are associated.

Prints from 86 persons were analyzed by dermatoglyphic studies. Forty-nine clinically certain mongoloid idiots were diagnosed correctly, as were twenty-seven normal controls. Of the remaining ten, unequivocal disagreement occurred four times and partial disagreement three times. The clinical diagnosis itself was uncertain in three cases. Hence the palmar stigmata yielded diagnoses as accurate as clinical diagnoses in seventy-six out of eighty-three patients.

Ideal Stumps and Prosthetics for Amputees

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Success in amputation surgery is achieved only after prosthetic fitting has been completed and the patient has been rehabilitated. Prosthetic fitting requires the coordinated efforts of the surgeon and the limb-fitter. The latter has a preference for certain classical levels of amputation because of ease of fitting and because standard devices have been made to fit these stumps. This preference has sometimes led to reamputation at higher levels in order to obtain what is considered an ideal stump. In actual practice, reamputations should be performed only for surgical indications such as infection, scar tissue, and circulatory disturbance. As a rule, a stump in excellent functional condition should have a prosthesis fitted to it rather than have the stump revised to fit a particular type of prosthesis. Many cases with wrist disarticulation, short below-elbow stumps, short below-knee stumps, and knee disarticulation have been functionally superior to higher levels because the length and contour of the stump has provided control of the prosthesis which was not otherwise possible. With increasing improvement in prostheses and with diligent effort, these cases can be well fitted.

As much of the extremity as possible should be saved at the time of an open amputation. Likewise, in a definitive amputation or revision, as much length as possible should be conserved, observing the necessity for good soft tissue coverage and a clean, healthy stump. The one exception to this rule is in the area between the level of a Syme amputation and the mid-leg. The long leg stump is not as desirable as amputation at or above the middle of the leg. With this possible exception amputation is seldom justified at a higher level than otherwise necessary in order to facilitate fitting.

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The amputation stump should assume its function of propelling a prosthesis as soon as possible after amputation in order to toughen weight-bearing points, to develop muscle power, and to preserve joint motion. A prosthesis can ordinarily be fitted about six weeks after amputation or revision if primary healing occurs. The early use of a prosthesis toughens the stump to a firm, healthy condition free from edema or excess tissue. If fitting and training are unnecessarily delayed, the amputee adapts himself to the handicap of the loss of a limb and he is not likely to become proficient in the use of a prosthesis.

THE stump is prepared for a prosthesis by firm bandaging with an elastic type of bandage, which is applied daily or oftener and which should be anchored above the next joint, especially if the stump is short. Active exercises are practiced with increasing resistance in order to develop weak muscles that are essential for proper use of a prosthesis, such as the deltoid, gluteus maximus, thigh adductors, and quadriceps. It is especially important to prevent joint deformity during convalescence. The use of massage has largely been abandoned in favor of bandaging, exercise, and early fitting.

The stump undergoes shrinking after fitting, so that the socket is soon too large and refitting is required. The longer the period of preparation before fitting, the less change will occur subsequently. However, the use of a prosthesis is by far the best method of shrinking and training the stump. Less change occurs in the upper extremity than in the lower, and the first prosthesis may be the permanent one. In the case of the lower extremity, however, repeated fitting is necessary during the first year. A lack of limb-fitting facilities or economic conditions may require the use of a temporary plaster pylon or temporary leg. A provisional leg with a standard design and adjustable features facilitates the fitting of a large number of amputees, especially in wartime. If adequate materials, skilled labor, or cost need not be considered, the same objective can be attained by the replacement of at least the socket of the permanent prosthesis as occasion demands.

The early training and fitting of the amputee requires close cooperation between the surgeon, limb-maker, physical and occupational therapists, and the patient. The program should be closely supervised by the surgeon responsible for the case.

LOWER EXTREMITY

Mechanism—A pylon is quite satisfactory for a Syme or below-knee stump, but it is an *undesirable* substitute for a provisional or permanent limb in the case of an above-knee amputation stump. The importance of a knee joint with friction control and of a carefully fitted hip control in developing proper walking habits make it desirable that these features be provided the above-knee amputee as early as possible. Pylons will, however, be useful where geographical or economic conditions require their use beyond the early postoperative period. (Figures 1 and 2.)

The knee joint for the thigh amputee should have stability on weight-bearing, ease of control, and durability. Some knee joints are made

Figures 1 and 2. Pylon for a Syme or above-knee stump.

to resemble the normal action of the human knee. Stability on weight-bearing (Figure 3) is important for the new amputee because if the knee buckles he falls down. The ideal knee would lock automatically on pressure at various degrees of flexion and still not interfere with normal activities such as sitting or descending stairs. Advances are being made in the use of new methods of hydraulic and mechanical control. Simplicity, durability, and ease of repair and replacement should be considered in the selection of the proper mechanism, but these factors should not prevent the progressive use of new and improved devices.

Hip control and harness—Formerly, the above-knee prosthesis was secured to the body by a shoulder harness which is still in use in some countries and by some of the older amputees in this country. The shoulder harness fails to give firm control of the prosthesis. A more important objection to the harness is the faulty gait which develops since the amputee lifts the prosthesis by raising the shoulder of the same side much higher than the other while he tends to come up on the toes of the normal foot. This shoulder-hunching gait is very conspicuous and undesirable. A harness may be required in addition to a hip belt, especially in the bilateral case, but its use has otherwise been abandoned in favor of the metal hip control.

Deformity—If a stump has flexion or abduction contracture, the socket must be fitted in the relaxed position of deformity, and then the rest of the prosthesis is fitted to compensate for the deformity. Deformities must be corrected before fitting, or they must be fitted as deformed. The prosthesis does not correct a deformity.

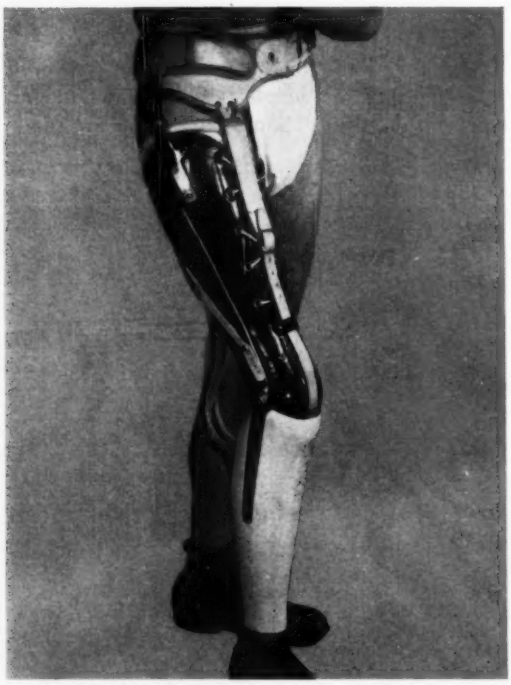


Figure 3: Knee joint for thigh amputee—should have stability on weight bearing, ease of control and durability.

THE usual deformity in the below-knee stump is a flexion contracture of the knee joint so the joint cannot be completely extended. The socket must be made to fit the long axis of the stump and the axis of the leg below this level changed to align it properly for weight-bearing. Some fitters fit the below-knee stump in very slight flexion as a method of choice. A stump that has 45° flexion contracture can be fitted satisfactorily in this manner, preserving the remaining knee motion for flexion and extension of the prosthesis. Very short flexed stumps can be fitted with a "bent knee" prosthesis, in which the patient kneels in the socket, which is shaped posteriorly to accommodate the end of the stump. This makes an excellent end-bearing or true knee-bearing prosthesis which is functionally superior to an amputation at a higher level.

An amputation through the thigh is ordinarily fitted with an ischial-bearing prosthesis so that the amputee sits on the socket, bearing his weight on the ischial tuberosity. If the amputation is at or above the level of the perineum it requires a "tilting table" type of prosthesis in which the socket fits the hemipelvis and the prosthesis is propelled by a

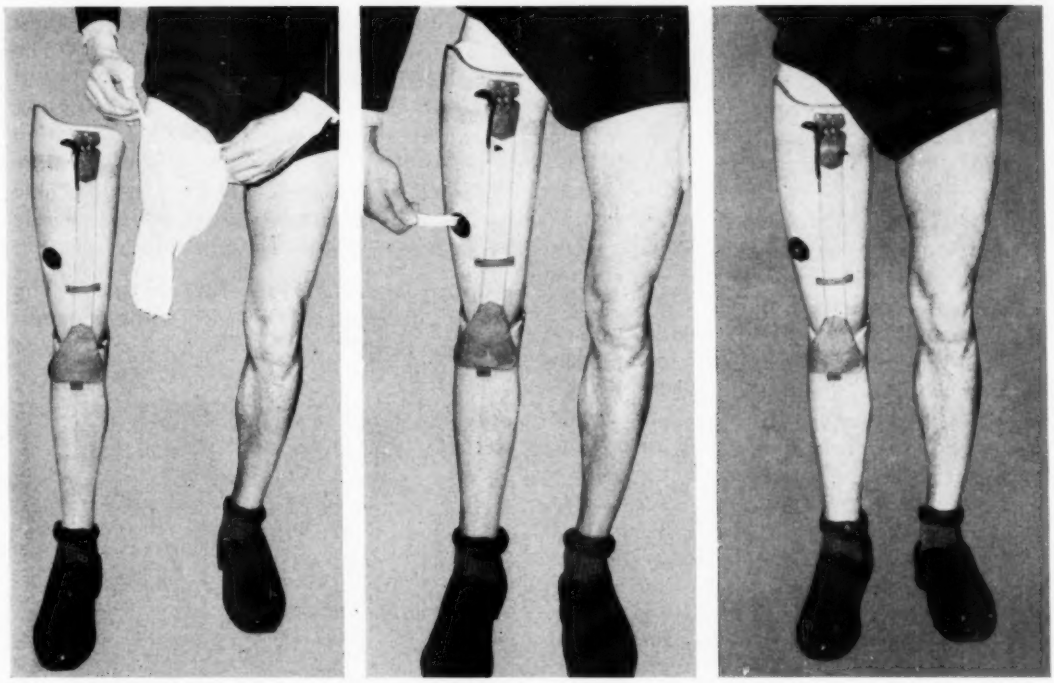


Figure 4: The stump is inserted with a thin stump sock which is then pulled out through the valve opening, thereby pulling the stump down firmly in the socket (figure 5) before the valve is closed (figure 6).

pendulum action, since there is actually no stump to propel it.

The end-bearing thigh stump resulting from amputation through the lower end of the femur should be fitted with an end-bearing socket, unless there is some contraindication to weight-bearing at this point. Some manufacturers prefer to make the ischial-bearing socket rather than build a proper end-bearing prosthesis because the long stump interferes with the standard knee control.

From the prosthetic standpoint, knee joint disarticulation has not been popular in the past. Amputation at this level is not common because below-knee or end-bearing above-knee (transcondylar) levels are preferred for fitting. However, a knee disarticulation which is covered by good skin can be fitted on the same principles as the other end-bearing or bent-knee stumps, and the level alone does not indicate reamputation. A properly fitted knee disarticulation is an excellent functional stump. To date, the end-bearing stumps have had to be fitted without the friction knee control desired in above-knee prosthesis, because a suitable mechanism has not been available. No doubt this will be available for end-bearing prostheses in the near future. In the meantime the advantages of a good end-bearing stump should not be sacrificed for the sake of fitting a knee control.

The suction socket—The suction socket is widely used for above-knee amputees in Germany but has had little application elsewhere. The socket is accurately fitted to the stump and provides ischial weight-bearing as described previously. Below the end of the stump the socket has a valve which permits air to escape when the stump is inserted. Then on closing

the valve the socket is airtight so that lifting the stump or pulling on the leg tends to produce a suction effect due to the force of atmospheric pressure. The stump is inserted with a thin stump sock which is then pulled out through the valve opening, thereby pulling the stump down firmly in the socket before the valve is closed. If the socket is properly fitted and the stump is in good condition, it gives the amputee firm control of his leg without the use of a pelvic belt and, in fact, the prosthesis cannot be pulled off manually without opening the valve. Only the short stumps, four to five inches in length, use any support, consisting of a harness or belt. The skin is in contact with the socket without any intervening sock, but there is no ill effect if the socket is properly finished. Stumps that are imperfect surgically may suffer edema and ulceration as in the case of conventional sockets. The satisfaction expressed by users of suction sockets indicates that this method of fitting deserves more attention than it has received heretofore. (Figures 4, 5, and 6.)

THE below-knee (B-K) prosthesis is used for all below-knee stumps between the level of the knee-bearing and the Syme stump. If the stump is in good condition and has undergone proper shrinkage and training, all the weight can be borne on the socket. The thigh corset gives some support, but its purpose is not to bear the weight (Figure 7) by tight lacing since this interferes with circulation of the stump and produces atrophy of the thigh. In below-knee stumps that cannot tolerate full weight-bearing, the stump has great value in controlling and propelling the prosthesis. In these cases the stump can be protected for a long period of usefulness by fitting a molded ischial-bearing thigh corset so that all or most of the weight is borne on the ischium while the leg stump is used only for control.

The Syme amputation is performed through the tibia and fibula immediately above the articular surface of the ankle. The end of the stump is covered by the heel skin which must be in good condition for weight-bearing. The Syme stump bears all the weight on the end and is fitted with a prosthesis that does not extend above the knee. The Syme amputation is the best and most serviceable stump in the lower extremity. It is, however, not suitable for women for cosmetic reasons because the ankle region is bulbous and conspicuous.

Fitting and training of the amputee—The proper fitting of the amputee is the responsibility of the limb-maker. The great importance

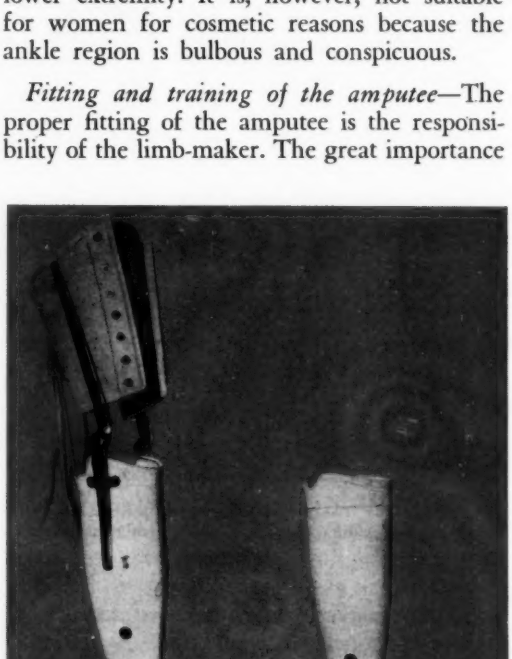


Figure 7: The thigh corset gives some support but its purpose is not to bear the weight by extremely tight lacing since this interferes with circulation of stump and produces atrophy of thigh.

of proper fitting has unfortunately overshadowed the equal importance of better materials and of mechanisms of improved quality and design. The basic principles of fitting are well established, but as new developments are made in material and design, new techniques of fabrication and fitting must follow. For

successful use of a prosthesis the socket must fit the stump without causing pain or constriction. In the case of the thigh stump the socket should fit snugly on the lateral surfaces while the ischial seat takes the body weight on the tuberosity of the ischium. Proper weight-bearing can be tested by inserting the finger between the ischium and the socket. When the body weight is applied, it will normally rest on the finger. Pressure must be relieved from the perineum without causing the tissues to roll over the edge of the socket since painful pressure in this region will cause the amputee to walk with a widely abducted and awkward gait. If the socket is too large after application of three stump socks, it should be replaced or be lined.

The below-knee stump is the most difficult to fit because weight is taken on a relatively small surface area and on tissues not accustomed to bear weight. Painful areas must be relieved of pressure while the weight is equally distributed over the remaining surfaces of the stump and the thigh cuff. The back of the socket should provide space for the hamstring tendons but should come as high in the popliteal space as full knee flexion will permit, while anteriorly the socket comes to the inferior border of the patella. The socket must be longer than the stump and exert uniform pressure in order to prevent terminal edema. A properly fitted socket will fit the stump in only one position. Any change in rotation of the socket requires refitting in relation to the joints and the container that holds it. The hip, knee, and ankle joints must be properly aligned to enable the amputee to walk with a smooth gait in which there is no abduction or rotary motion of the prosthesis. It should not be necessary to twist the pelvis into any abnormal position to permit direct forward propulsion of the limb.

The length of the prosthesis should correspond to the normal extremity. No exception should be made to this rule in the below-knee or long thigh stump. Short thigh or hip stumps may require one half to one inch shortening to facilitate the pendulum action without raising the pelvis on that side.

Instruction in the use of a prosthesis—The amputee should receive training by qualified instructors as soon as he is fitted with the prosthesis. Special facilities are desirable in physical therapy, especially for the lower extremity amputee, and in occupational therapy, especially for the upper extremity amputee. It is recommended that at first the prosthesis be worn for only a short period daily so that the stump may become gradually adjusted to the socket. Excessive use early will cause the stump to become irritated and painful. When the leg is removed, the stump should be firmly bandaged with an elastic bandage or swelling will occur and the stump will be too large the following day. The prosthesis should be kept in the clinic and worn only under supervision until the amputee becomes proficient enough to use it independently without developing faulty habits. The stump should be carefully examined for evidence of muscle weakness and imbalance and for evidence of joint contracture since muscular strength and normal joint motion are essential. The normal extremity and the spine should be flexible and the posture should be as nearly normal as possible.

Where a large number of amputees are undergoing training, they are best divided into sections according to the level of amputation. Special provision is made for bilateral and other unusual cases. The use of individual movies offers an excellent medium for training, since this gives the amputee an opportunity to analyze his own faulty habits and to observe his progress.

THE UPPER EXTREMITY

The hand mechanism—A hand may be of a mechanical or cosmetic type. Mechanical hands lack a satisfactory cosmetic appearance and require a glove for covering which makes them conspicuous in the summer when gloves are not worn. Mechanical hands, unfortunately, have also lacked functional value and have been heavy. Hands have been made of wood,

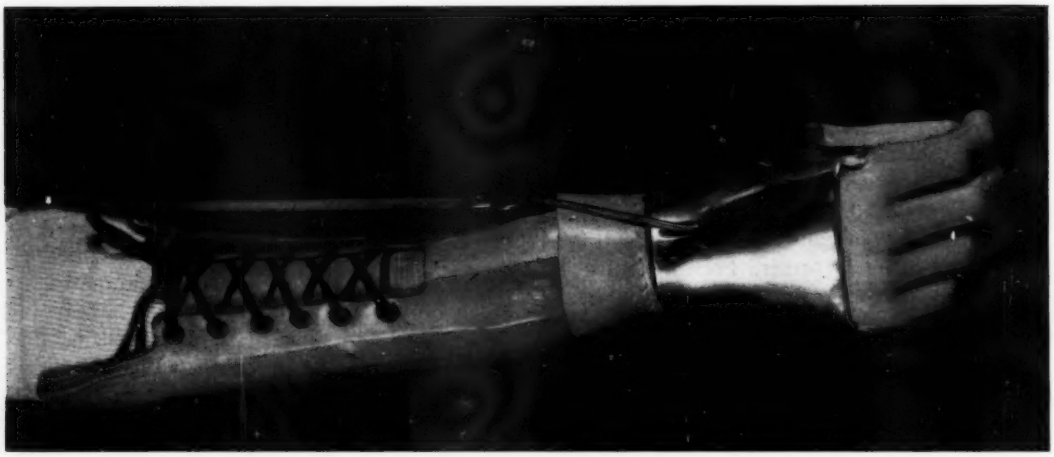


Figure 8: Hand (Miracle), made with an aluminum palm, rubber thumb and fingers, articulated at the metacarpal phalangeal joints; provides active closing and passive opening.

metal, rubber, or a combination of metal and rubber. Wooden hands are usually articulated in the thumb alone or in the thumb and fingers at the metacarpal phalangeal joint and are opened by action of the cord, closing passively by spring action. One type of hand (Becker) contains thumb and fingers of coiled wire with rubber finger tips all activated in that way. (Figure 8). The miracle hand, which is made with an aluminum palm and rubber thumb and fingers, articulated at the metacarpal phalangeal joints, provides active closing and passive opening which is more desirable since closing the hand is normally a more important and delicate motion than opening. Only the double motor cineplastic prostheses described below provide both active flexion and extension of the fingers and thumb.

Until recently no serious attempt has been made to construct a cosmetic hand. Now, however, good cosmetic hands are being made of rubber and of plastic materials. These match the normal hand, but durability of the color and material is still limited. The cosmetic hands have not had any functional value and few experimental attempts have been made to combine mechanical and cosmetic features in the same hand. Replacing the human hand with an artificial one presents a problem much more difficult than replacing a leg because the latter is relatively simple and less conspicuous. Until recently research in this field has not kept pace with modern industry. While improved devices are now being produced, they are still in the laboratory stage and further developments, improved manufacturing, and new fitting methods are still required.

The hook—Mechanical hooks (Figures 9 and 10) have great utility value for the amputee and are essential for the bilateral case. A hook is very conspicuous and objectionable to many amputees, but its functional value makes it desirable that all cases be trained in its use early during convalescence. The hook can readily be interchanged with a cosmetic hand for dress purposes.

VARIOUS hooks have been designed but they may be classed as rigid and split types. Of the latter, the Dorrance type is the most popular. Split hooks are almost unknown in Continental Europe, though used extensively together with other mechanical tools in this country and in Great Britain. The hand or

Figures 9 and 10: Mechanical hooks have great utility value for the amputee and are essential for the bilateral case.

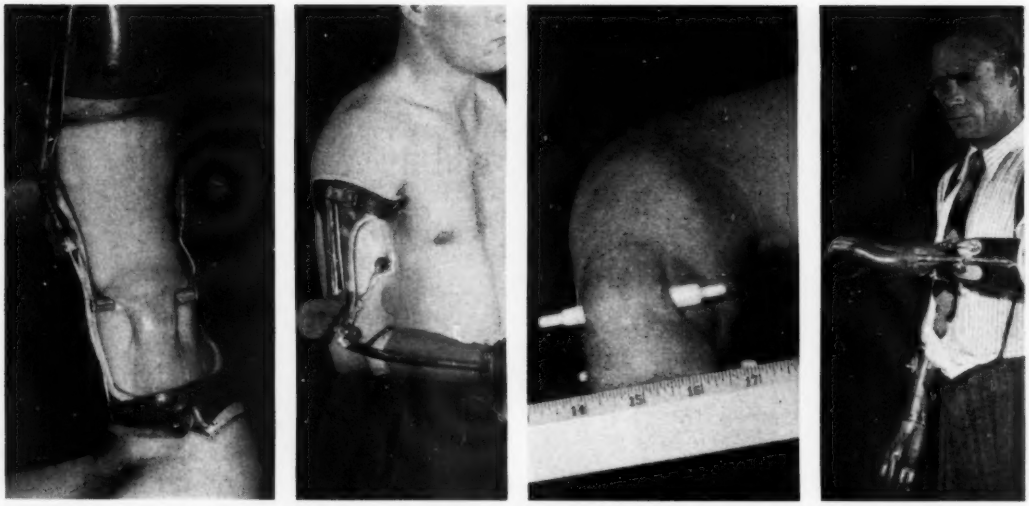
hook is activated by a cord attached to the harness around the opposite shoulder, except in case of the cineplastic amputation. An improved cord designed by Northrop Aircraft, Inc., consists of a multiple-strand wire cable contained in a flexible metal housing. It readily transmits force around the curves without serious mechanical interference. Pneumatic, hydraulic, and electrical methods of control have not had practical application to date.

The wrist mechanism—The best wrist mechanism at this time for the forearm stump is a lightweight metal rotary wrist designed by Northrop Aircraft, Inc. This device is useful in case of amputation through the middle or distal third of the forearm. It requires a double plastic socket; the inner or true socket fits the stump and is attached to the driving mechanism of the wrist, which rotates within a metal casing; this, in turn, is attached to the outer section of the forearm. A system of locking rollers in the wrist, controlled only from the proximal end, prevents rotation from the hook end but permits the stump to control the rotation with ease. The mechanism can be adjusted to lock as above or the locking rollers can be removed if desired. The unit can be made so that the hook will rotate through the same arc as the stump, or the ratio can be increased to nearly 2½ to 1. Rotary wrists have previously been used in several types of above-elbow prosthesis by providing automatic rotation on elbow flexion.

The elbow mechanism—An improved metal elbow joint of lightweight and excellent construction has also recently been developed by Northrop Aircraft, Inc., for above-elbow amputees. This provides locking and unlocking in any position and is controlled by shrugging the shoulder. The mechanism is bonded to a plastic socket above and to a plastic forearm below.

Shoulder amputations—Interscapulo-thoracic or forequarter amputation leaves a marked asymmetry, since the sloping chest wall has no covering except skin and subcutaneous tissue. A complete prosthesis is not indicated because there is no stump to support the prosthesis. However, a light shoulder pad contoured to fit the body and to match the other shoulder will greatly improve the appearance. Amputation between the shoulder joint and the lower border of the pectoralis-major tendon leaves no stump of functional value in activating a prosthesis. However, a cosmetic arm with very limited functional value can be suspended by a socket fitted over the shoulder. This is made of molded leather or preferably light plastic material and held in place by straps around the chest and other shoulder. The rest of the prosthesis should be as light as possible. The hook can be operated from the opposite shoulder, but the amputee should not expect to find this prosthesis very useful. Many amputees have found that a prosthesis fitted at this level is more of a burden than a benefit.

Short arm stumps are better fitted with a short working prosthesis than with the conventional full-length type. The latter can be made detachable just below the socket so that a working tool can be inserted, thereby giving greater efficiency than if the tool is attached at the level of the wrist. The British have used



Figures 11, 12, 13, 14: Cineplastic amputation utilizing individual muscles or muscle groups to activate a prosthesis independent of the general movement of the stump itself. This is accomplished by the construction of motors, or skin-lined tunnels through the muscles, to which the prosthesis is attached.

this principle to greater advantage than others. For cases having an intact pectoralis major, a cineplastic motor through this muscle offers considerable benefit as a holding mechanism and as a source of power.

The arm stump—A minimum stump length two inches below the pectoralis major is desired for a satisfactory fitting. The socket is made of wood, aluminum, leather, or, preferably, plastic. The material should be strong, light in weight, and silent on contact with external objects. The actual choice between materials that meet these requirements is a matter of individual preference. A plaster mold of the stump is covered with two or more layers of stockinette impregnated with a thermosetting resin. The elbow assembly is aligned in the proper axis in relation to the stump and is incorporated in the lower end of the socket corresponding to the level of the normal elbow.

AMPUTATION through the condyles of the humerus leaves the end of the stump broad and flat. This level may make fitting more difficult because of a bulbous end, but the contour of the stump enables the amputee to control the prosthesis much more effectively than in the case of a tapered stump. As in the case of the long thigh stump, the length here may interfere with fitting of a desirable joint assembly but the advantages of the long stump outweigh the advantages of a special mechanism.

The forearm stump—As much of the forearm as possible should be conserved for prosthetic fitting. The functional value of the stump is measured from the biceps tendon downward, but a stump at or above this level still has value in stabilizing and controlling the prosthesis. The functional length of the stump can be increased for fitting purposes, by cutting the biceps tendon leaving only the brachialis muscle for elbow flexion. However, the biceps should not be cut for the purpose of fitting if a biceps cineplastic motor is contemplated at a later date. The forearm socket is cut out of wood or is fashioned over a mold of the stump using aluminum, leather, or plastic. By various combinations of plastic materials the degree of hardness and resonance of the socket can be

controlled. If the rotary wrist is used, an inner socket and an outer container are required; the former is attached to the driving mechanism of the wrist, while the latter holds the outer casing and elbow joints.

Amputations through the carpal bones or wrist joint have in the past often been subject to reamputation at a higher level in order to obtain what was considered an ideal stump for fitting, since the longer stumps fitted by conventional methods tended to make the prosthesis longer than the normal side. However, it is recognized that the ability to rotate the longer stump without the use of a special mechanism is of great practical value. If the wrist stump is in good condition from the surgical standpoint, it can be fitted by a simple flexible or rigid leather or plastic socket. No retention cuff is necessary above the elbow, and a very simple harness is required to support the activating cord.

CINEPLASTIC AMPUTATIONS

A cineplastic amputation utilizes individual muscles or muscle groups to activate a prosthesis independent of the general movement of the stump itself. This is accomplished by the construction of motors, or skin-lined tunnels through the muscles, to which the prosthesis is attached. The practical application of this procedure has been limited to the upper extremity, and its success depends on proper surgical technique, muscle training, and the fitting of a satisfactory prosthesis (Figures 11, 12, 13, and 14).

Cineplastic surgery has received little attention outside Germany. Its use in the United States has been limited to the work of H. H. Kessler of Newark and Nissen and Bergmann of New York. Only one manufacturer in this country has supplied the prosthesis. At the end of World War II interest in this subject was again renewed because of the observation by American surgeons of the work of Lebsche in Munich. Lebsche has performed more than 500 cases, and his surgical technique and functional results merited special study. Therefore, a War Department Commission, including the author and other representatives of the Surgeon General's Office and the Committee on Prosthetic Devices, visited Europe in March and April, 1946, for a study of amputations and prostheses including cineplastic methods. This Commission reported:

"CINEPLASTIC surgery at the pectoral, arm, and forearm levels has reached a high degree of perfection in Professor Lebsche's clinic in Munich. With proper attention to technical details and with careful postoperative training, excellent results can be obtained in properly selected cases. Meticulous surgery, the use of large skin tubes, and the liberation of the distal end of the muscle in all cases contributed to the superior results observed in his cases in comparison to those observed elsewhere. A number of cases which had been performed outside Munich or Berlin were unsatisfactory because of improperly placed tunnels, small tunnels, and necrosis of the skin. The wide range of excursion and the considerable strength in the better cases should prove of great value in further development of cineplastic prostheses."

The commission recommended as follows:

"1. That cineplastic surgery be approved for properly selected upper-extremity amputees according to the technique of Professor Lebsche. A number of carefully controlled cases should be performed in order to perfect the cineplastic prosthesis and to determine its value in this country.

"2. That the Krukenberg amputation be approved for properly selected bilateral upper-extremity amputees, with special application in the blind.

"3. That arrangements be made to obtain from Munich three or four cineplastic amputees of various types in order to demonstrate the value of the operation and in order to test redesigned prostheses. Similar cases could be produced in this country but the necessary surgery and postoperative training would delay the program at least six months.

"4. That intensive research be conducted to develop cineplastic prostheses which will provide to the amputee the maximum benefit from this type of surgery. This should include the development of an interchangeable hand and hook."

Following this report three amputees were procured as recommended. They visited the various Army Amputation Centers and served as test subjects in the research projects under the Committee on Prosthetic Devices.

Principles of cinematization—In the standard type of amputation the muscles that originate in the stump cease to function and motion of the stump is accomplished only by those muscles which insert above the level of the socket. In the cineplastic amputation, on the other hand, an effort is made to utilize the muscles which originate in or immediately above the stump and have usually lost their insertion, thus furnishing additional sources of power.

The following description of technique is based on observation of cases in the clinics of Sauerbruch in Berlin and Lebsche in Munich and include Lebsche's modifications of the Sauerbruch operation.

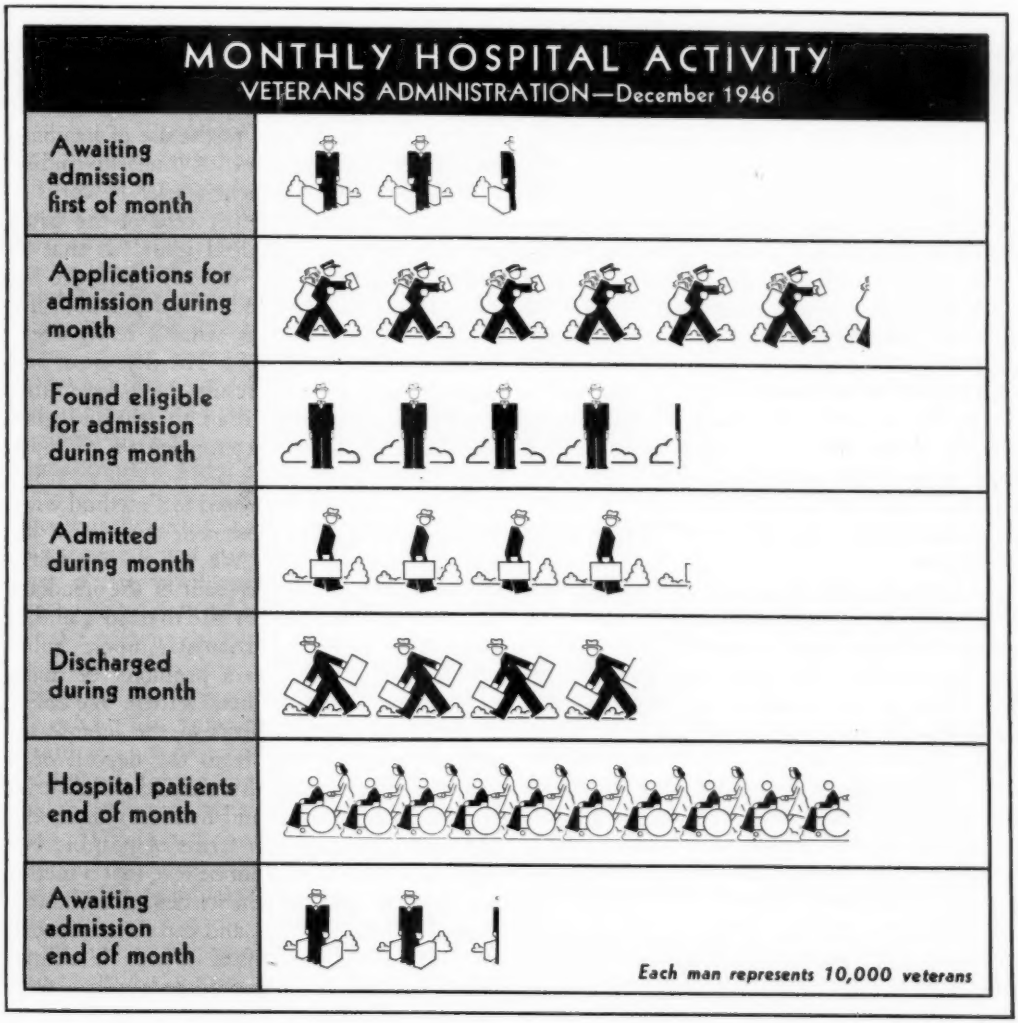
Technique—Cineplastic surgery should not be undertaken at the time of an emergency amputation. The stump should be well healed and free from infection or excessive scar tissue. The stump must be sufficiently long to have good contractile muscle through which to insert the skin tube at or below the middle third of the muscle since the force and excursion are in proportion to the length. The motor is constructed through the muscle belly, as low down as possible, but it is never made through the tendon and is not made on the end of the stump. Motors have been successfully employed in the pectoralis major, biceps, triceps, forearm flexor, and forearm extensor group of muscles. Ordinarily, in the forearm stump, separate motors are made through extensors and flexors; in the arm, through biceps and triceps. The pectoralis motor may be combined with one or more of the others or used alone in a short arm stump. Two motors act as antagonists in closing and opening the hand, but a single motor may be used to close the hand while a spring opens it passively. Where the forearm stump is too short for a motor, the biceps motor is constructed, saving the stump below the elbow for active elbow motion by the brachialis and triceps muscles while the biceps activates the hand. Holding motors are occasionally used in very short stumps to help hold the prosthesis in place without giving active motion.

Cineplastic prosthesis—The Sauerbruch prosthesis, which has remained essentially unchanged in recent years, consists of a standard metal and leather frame and a wooden hand with fingers and thumb articulated at the metacarpal phalangeal joints. Extension may be passive by spring action or preferably active by an extensor motor. Force is transmitted from ivory pegs inserted through the tunnels by means of chains or cords to the hand. Cineplastic surgery has been highly perfected, but the prosthesis requires further development in order to utilize the available muscle strength with greater efficiency.

Krukenberg amputation—The Krukenberg operation consists of splitting the forearm stump into radial and ulnar rays which act as the prongs of a pincer when the radius closes on the ulna. This requires a forearm stump with a minimum length of 17 cm. (6.7 inches) measured from the tip of the olecranon. The forearm is split between the radius and ulna proximally to a point about 8 cm. (3+ inches) from the olecranon, preserving the radial and ulnar vessels. The removal of some muscle groups is optional, but results are equally good, and perhaps better, without their removal. The incision is made to permit closing the skin on the radial portion and the remaining defect on the ulna is covered with a free split graft or a pedicle graft from the abdomen. This amputation gives the patient power to grasp with a device which has tactile sensation, and it therefore has its greatest usefulness in blind

bilateral forearm amputees. It is also useful in other bilateral amputees who have one forearm suitable for this procedure. If desired, the stump can be fitted with a standard prosthesis for cosmetic or other special purposes. The Krukenberg operation has been done on approximately 1,000 cases in Germany.

Figures 1 through 10 from: Museum and Medical Arts Service, Army Medical Museum. Figures 11 through 14 from: Army Medical School, Photographic Laboratory, Washington, D. C.


MONTHLY HOSPITAL ACTIVITY
VETERANS ADMINISTRATION—December 1946
Awaiting admission first of month
Applications for admission during month
Found eligible for admission during month
Admitted during month
Discharged during month
Hospital patients end of month
Awaiting admission end of month
Each man represents 10,000 veterans

DIAGNOSTIC CLINIC

Thiouracil, Thiobarbital, Propyl Thiouracil and the Treatment of Hyperthyroidism

FRANK H. LAHEY*

LAHEY CLINIC, BOSTON

THERE has been so much discussion, written and spoken, and considerable disagreement and confusion concerning the use of the thiourea group of drugs in the treatment and preparation of patients with hyperthyroidism for surgery that I thought you would like to hear about our practical experience with these drugs. I understand that you have had expressed to you some opinions of the value of thiouracil as a substitute for surgery, and I should like to present our views and the reasons why we differ. We feel very strongly, and I think there will be more and more evidence to indicate that thiouracil, thiobarbital, and propyl thiouracil are not to be safely used as substitutes for surgery.

I should also like to discuss another method of treating hyperthyroidism and to state our reasons for opposing it, namely, the use of irradiated iodine. The basis for using irradiated iodine in the treatment of hyperthyroidism is the fact that if a given dose of iodine is administered to a patient, of that iodine 80 per cent will be accepted by the thyroid gland. Therefore, the principle of the use of isotopes, as proposed by the Lawrences in Berkeley, such as the exposure of phosphorus in the cyclotron and the intravenous use of irradiated phosphorus, was transferred to the use of irradiated iodine in the treatment of hyperthyroidism.

How does the treatment work? It works literally by depositing 80 per cent of the irradiated iodine in the thyroid gland so that the radiation effect will be directly upon the thyroid gland and thus produce a depression of its activity. In simple terms, what it really does is literally to fry the thyroid. The deposit of radiation in thyroid cells results in a fixed, firm, hard state of thyroiditis in the thyroid gland which brings about varying degrees of inactivation and destruction.

We personally are opposed to a method which by hit or miss accomplishes destruction of thyroid tissue irrevocably. We believe in addition to this that since 20 per cent of the irradiated iodine is not accepted by the thyroid gland, its long-range results, particularly upon kidney tubules and possibly as a promoter of malignancy, have as yet not been settled. We believe that the long-range effects of the intense thyroiditis which results from the deposit of irradiated iodine in the thyroid and the cicatrization and later fibrosis and fixation which occur are as yet unproved in terms of possible later complications. We do not believe that a method which is as uncertain in its degree of destruction of thyroid activity, and certainly unproved and unseasoned in terms of its possible ultimate complications, can be compared with a surgical method, subtotal thyroidectomy, which we will submit to you has now, with the use of

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thiouracil, thiobarbital, and propyl thiouracil, had its mortality reduced to 0.17 per cent. It is about these three drugs that I wish to speak.

I should like to say now that we have abandoned thiouracil and thiobarbital entirely because they have such a high percentage of complications, and we now employ only propyl thiouracil. The incidence of disagreeable and dangerous complications from the administration of thiouracil is 9 per cent; the incidence of complications from the employment of thiobarbital is 28 per cent; and the incidence of complications from the employment of propyl thiouracil is 2 per cent (1 patient had a fever reaction; 5 patients had white cell depression, 1 of whom developed agranulocytosis) in 210 patients prepared for surgery and 90 more still under preparation. The incidence of complications of propyl thiouracil is so low that we have abandoned the other two drugs except under circumstances of which I shall speak.

The patient mortality in 25,000 operations for thyroid disease is 0.88 per cent and the operative mortality 0.75 per cent. Since the use of thiouracil in July, 1943, and now propyl thiouracil, mortality has dropped to 0.27 per cent, using one of these three drugs to prepare patients with hyperthyroidism for surgery, and in the last year it was 0.17 per cent, the one death being a case of thrombosis. In the first ten months of 1946 there have been no deaths, so that the present operative mortality figures in 670 patients with toxic goiter prepared for surgery is 1 death (coronary infarct).

I would like now to review quickly how these drugs act. We know that from the pituitary gland comes the stimulating hormone which produces hyperplasia in the thyroid gland. We do not, however, know how this group of thiourea drugs accomplishes its effect, which is to inhibit the synthesis of thyroxin completely even in the presence of a histologic appearance of the thyroid gland of hyperthyroidism, that is, hyperplasia. We know that the protein-bound iodine which represents the synthesized thyroxin diminishes hand in hand with the improvement in clinical symptoms and the basal metabolism. We know that the hyperplastic cell which characterizes the histologic appearance of hyperthyroidism persists in spite of the fact, as already stated, that the metabolism comes to normal, and this is of particular importance to the surgeon.

I have frequently said, after operating upon patients with hyperthyroidism who were prepared for surgery solely with thiouracil, never having had any iodine, that if I had to operate on patients so prepared, I would prefer to give up thiouracil. The reason I make this statement is that in patients prepared solely with thiouracil, as all surgeons know, the gland is still hyperplastic, bleeding is terrific, and the gland will not hold hemostats, double hooks, or ligatures, and it is next to impossible to control the bleeding and to do anatomical dissection.

We have devised and for the past two years have practiced the plan of combining iodine with the thiouracil, and now propyl thiouracil, to produce an involution that devascularizes the gland, compacts its epithelium, and makes conditions which are much more ideal for surgery.

In the beginning of our experience we stated that these patients should have thiouracil during the first of their period of preparation and only during the last three weeks of preparation should they have Lugol's solution. We have now changed that so that they now receive Lugol's solution and propyl thiouracil throughout their period of preparation. This has prolonged the period required to bring their metabolism to normal a little, but it has resulted in more prompt improvement in symptoms early in their preparation and complete involution and devascularization of the gland.

We have learned that the period of time taken to prepare these patients for surgery will vary in different types of thyroid glands. In patients with hyperthyroidism who have had the disease nine months or less and who have not taken iodine, there will be an average daily drop in metabolism of about 1.3 per cent. If iodine has been taken, the drop in metabolism will be at the rate of about 1 per cent per day. If the hyperthyroidism is over one year in du-

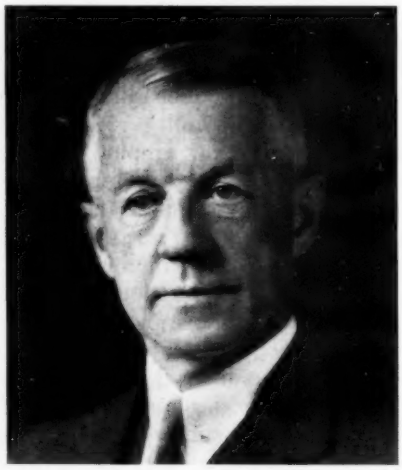
ration, irrespective of iodine, this drop will also be at the rate of about 1 per cent per day. In the patients with large, toxic adenomas, however, particularly in those who have had iodine, there will be a slower rate of drop in metabolism, approximately 0.5 per cent per day, and the longest time we have ever taken to get the elevated metabolism of a patient with a toxic adenoma to normal is 180 days.

In general, in exophthalmic goiter it can roughly be said that it will take the number of days to bring the metabolism to normal that it is above normal.

We have repeatedly been told by visitors that they are unable to bring the metabolism in these patients to normal. In our opinion, this is due to the fact that either they do not give enough of the agent or they do not give it long enough, or, still further, there may have been a complication, because in no case have we failed to bring the metabolism to normal when we have given it long enough.

I think there have been a good many misleading statements in the literature concerning these drugs, particularly propyl thiouracil. It has been stated that administration of propyl thiouracil does not result in any complications. That is not true. We have had 5 cases of white-cell depression, in 1 of which agranulocytosis developed, and 1 case of fever reaction. It is our opinion that if one uses large enough doses of propyl thiouracil to bring the metabolism to normal, that is 200 mg., there will be an occasional depression in the white and differential counts.

WE HAVE frequently been asked, "How often must white and differential counts be done?" Probably the safe period is approximately once a week or once in ten days. We have often also been asked, "At what period should one cease administering these agents as relates to the white count?" When the white count has fallen as low as 4,500 and when the granulocytes are found to be reduced to 45 per cent, further administration of these agents should be discontinued and the patient should be carefully watched for further drop.



Frank H. Lahey

One other thing to be noted is that in the preparation of patients with propyl thiouracil for surgery, no propyl thiouracil is given for the last week. The reason is that we have seen agranulocytosis appear one week after the last dose of the drug has been administered, and we do not wish to have to deal with the complication of an agranulocytosis which comes at the time of the operation or during the period immediately afterward.

Multiple-stage operations have disappeared in the last three years during which time we have employed this drug. The mortality has progressively dropped to 0.17 per cent. We have recently reported our experiences with 25,000 thyroid operations upon 22,000 patients. The operative mortality in the 25,000 operations was 0.75 per cent and the patient mortality 0.88 per cent. During the last three years since we have been preparing these patients for surgery with one of these three agents, thiouracil, thiobarbital, or propyl thiouracil, the mortality has dropped to 0.25 per cent, in the last year to 0.17 per cent and in the first ten months of 1946 to 0. We have now prepared 660 patients for surgery with one of these three agents with but one

death, and that a coronary thrombosis which occurred on the second day after the patient had made an excellent operative recovery from the subtotal thyroidectomy.

A very graphic example of what these patients can do is illustrated by a patient whom I have often described. She was a lady of 77 with 30 pounds weight loss. She had auricular fibrillation, heart failure, and was a diabetic. She had a metabolism of +44. She would have been a very bad risk prior to the time these drugs were available, but when she was put on thiouracil, the metabolism dropped to +1, the heart became regular, her compensation was restored, the diabetes was easier to treat, she gained 8 pounds in weight, had a subtotal thyroidectomy, and at no time did she have a pulse rate over 80 postoperatively or a temperature reaction. If you will compare this patient with what the problems would have been prior to the employment of these agents, it will graphically illustrate how we have been aided in dealing with the patients who have serious complications, such as heart failure, diabetes, tuberculosis, pregnancy, or any of the other complications.

We have also learned that one cannot depend upon the time period for complications. We have seen patients go along with no difficulties whatever and then as late as the ninth month, develop an agranulocytosis. Note that these complications are: depression in the white blood cells and differential counts, fever, skin eruptions, edema of the skin, salivary gland reactions, and there has recently been reported a patient who developed a pancreatitis that required exploration because it is known that the administration of these drugs likewise promotes hyperplasia of the pancreas.

It has been stated that the present employment of thiouracil over the country has produced a mortality higher than occurs with good thyroid surgery. We believe one of the disadvantages of the prolonged administration of these drugs is that you cannot predict at what time an agranulocytosis may occur; the patients must always be in danger of this possibility and must always be close to adequate laboratories where they can have white and differential counts.

We have employed these agents in 21 cases to determine whether or not they would promote permanent remissions. In 8 young individuals with very low metabolisms who had had mild hyperthyroidism and had had it but a short time, permanent remissions have occurred, but in all of the others, reappearance of the hyperthyroidism has occurred as soon as the administration of these drugs was stopped.

Our own medical department believes that the percentage of recurrences on omitting these drugs is so high, that we do not feel interested in the use of this drug as an agent to be used as a substitute for surgery.

I do not mean particularly to be prejudiced in favor of surgery nor do I defend it against thiouracil, but wish only to compare it. Up to ten years ago we had a recurrence rate following subtotal thyroidectomy of 7 per cent, which was by far too high. We now have a rate which is under 1 per cent and the mortality rate, as has already been stated, is 1 death in the last 660 cases. We have practically abolished tetany and recurrent laryngeal paralysis. When one therefore considers our recurrence rate, the danger of the use of thiouracil in place of surgery, the risk of agranulocytosis, the necessity for frequent white counts, the fact that agranulocytosis can occur at any period of the administration, we believe that from our point of view, surgery continues to be the safest, most positive, and most satisfactory method of treatment.

We believe that it will be possible to give up thiouracil and thiobarbital now because propyl thiouracil is so much safer. In view of an incidence of 9 per cent complications with thiouracil, 28 per cent with thiobarbital, and only 2 per cent with propyl thiouracil, we believe the former two should be abandoned.

We would like again to stress that the combination of iodine throughout the administration of thiouracil is more effective in prompt action than the use of thiouracil alone.

We would like to call attention to the fact that when patients are sensitive to propyl thi-

ouracil one may occasionally change to thiouracil and carry them through without reactions.

When complications such as agranulocytosis or neutropenia occur, there is but one drug that can be depended upon, and that is penicillin. Pyridoxine (B_6) is of no value; liver extract is of no value. What happens when you get an agranulocytosis is that the bone marrow is unable to produce the protective elements in the blood to deal with it; therefore, you must use some agent to deal with the infection while, by omission of the thiourea drug, the bone marrow recovers its capacity. It is obvious that one must be particularly on the lookout for patients who have low white counts, below 4,500, and differential counts below 45 per cent neutrophils, and particularly those who develop sore throat.

I wish to stress again that pancreatitis has been reported, due to hyperplasia of the pancreatic cells, and during the administration of these agents one must watch for pain in the abdomen.

One other thing I would urge, although I think it is probably not very practical, is that, if possible, in any hospital where this treatment is being used, it should be put in the hands of one or two men. That means they get the experience with it so that they can protect the patients.

ANOTHER point to bear in mind is that the fever reactions which occur with these drugs are associated with joint pains, back pains, nausea, vomiting, and that they are true sensitization reactions.

Also of interest are two other thyroid conditions which we have encountered during the last year or two. They may occur in your experience and you should, therefore, be conscious of them. One is the thiocyanate goiter. Thiocyanates are known to be goitrogenic in character and are the kind of goiter that will occur in the experience of some of you before the year is over. Unless you know about it, you can be greatly confused and can get into difficulty with it. Potassium thiocyanate is being used, as you know, for hypertension. It is a goitrogenic agent; it will produce enlargement of the thyroid gland and will ultimately produce myxedema. It is like the thiourea group. We have had two of these types of thyroid enlargement incited by potassium thiocyanate. They produced so much enlargement well down to the mediastinum and compression of the trachea that until we found out what it really was, the patient was threatened with a tracheotomy.

Because it enlarges the thyroid and produces myxedema, the thiocyanate goiter can also definitely interfere with breathing. You must be on the lookout, therefore, for patients who have been under blood pressure treatment with potassium thiocyanate as to the possibility of a thiocyanate goiter and its producing interference with breathing.

You need only stop the treatment or give them thyroid extract; the gland will promptly go down and they will regain their ability to breathe all right.

The other type of thyroid disease has also occurred in the last two years and is the hyperthyroidism with a normal metabolism. How can it happen? In occasional cases the normal metabolism may be a minus one. We have had a patient who had a —34 who had no myxedema at all. She did not have a high blood cholesterol, but when her metabolism was at +4 or +5 she had hyperthyroidism. Her blood cholesterol was low, she had all of the clinical symptoms, and following subtotal thyroidectomy, with a return of the metabolism to —34, she was perfectly normal.

We have also had another case with a normal metabolic rate but with all the clinical signs of hyperthyroidism and with a low blood cholesterol, tachycardia, tremor, exophthalmos. When she had a subtotal thyroidectomy she too had convincing drops in metabolism to minus degrees, but this was her normal metabolism and there was marked clinical improvement.

Do not be misled at the inclusion of occasional patients who have very definite clinical hyperthyroidism because they can have a normal metabolism which for them is an elevated metabolism if their normal metabolism is of a low minus character.

DIAGNOSTIC CLINIC

Treatment of Pernicious Anemia

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This discussion will be limited to the treatment of pernicious anemia, a disease which is very poorly handled, although there is a specific for it. Five case histories will be set forth, and I shall make some comment about the diagnosis of the disease, tell you how I think it should be treated, and show you what results our patients have had with such treatment.

The first patient has been under my care since September 30, 1931. A diagnosis of pernicious anemia had been made in 1928, three years before I saw her. She could not have been treated very well, because when I saw her she had only a little more than a million red cells and 32 per cent hemoglobin. From 1928 to 1931, although the diagnosis of pernicious anemia was evident, she had had a hectic time with many ups and downs and had undergone thyroidectomy for tachycardia. The thyroidectomy was of no real value to her, since the symptoms for which the operation was done were caused by pernicious anemia.

She had had the usual signs of weakness and other symptoms of anemia, and during that period developed a cord lesion. When I first saw her she could hardly walk. She had such a marked involvement of the lateral columns of the spinal cord that she could only shuffle along; she could hardly lift her feet off the floor and was unable to walk upstairs at all. I emphasize the neurologic status because this case shows one greater danger of incomplete treatment and also shows what marked improvement one can get in the neurologic lesions of pernicious anemia with proper treatment.

She had a large spleen which is very unusual in pernicious anemia. In our series of more than 600 patients not more than 5 per cent have had an enlarged spleen. Splenomegaly is always against the diagnosis of pernicious anemia. She did have a very smooth, glossy tongue. The first thing that I do when examining a patient with anemia is to look at the tongue. I once thought that when a doctor looked at the tongue he didn't know much medicine. I now think that he knows a lot of medicine when he does.

In addition to the curious shuffling gait she necessarily had hyperactive tendon reflexes in the knees and ankles. She had a bilateral positive Babinski reaction and marked ankle clonus. The vibratory sense was entirely lost up to her hips.

Treatment was started by the method set forth below. Her blood quickly returned to normal and has remained normal for the last fifteen years. She comes in every little while for an examination and blood count. Her blood count has always been normal.

Before treatment, what did her blood show? There was an anemia with large red cells. The most characteristic thing about the blood in pernicious anemia is the large red cells. There is always a macrocytic anemia in an active untreated pernicious anemia. Not infrequently patients are treated for pernicious anemia when

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one glance at the blood under the microscope would rule out this disease since the red cells are not large.

She also had no free hydrochloric acid on the test meal. Of what importance is that? No patient with true idiopathic pernicious anemia ever has free hydrochloric acid in the stomach test meal. A test meal is one of the simplest things to try when one is confronted with a patient suspected of pernicious anemia. Any doctor can pass a stomach tube in his office and see whether the patient at the end of the hour has any free hydrochloric acid. If the patient has free hydrochloric acid, the patient could not have idiopathic pernicious anemia. This patient had marked neurologic changes and achlorhydria, so she had the three different characteristic phases of pernicious anemia. The first is the hematologic phase, which is the macrocytic anemia; the second is the gastrointestinal phase, which is a constant lack of free hydrochloric acid; the third is the neurologic phase, which is primarily the loss of vibratory sense and secondarily other neurologic changes.

The second patient has been under observation almost as long as the first. She has been so faithful that I can almost tell the day of the month from her visit. When she first came in thirteen years ago her trouble was neurologic.

IN 1930, three years before I saw her, she developed weakness and numbness in her hands and feet. A diagnosis of pernicious anemia was made. I cannot tell you what kind of treatment she had for those three years, but it was certainly not efficient treatment because when I saw her she still had a macrocytic anemia. The anemia was not as marked as the first patient's. The red-cell count was only a little over 2,000,000, however. She came in on a stretcher because she could not walk at all. Within a day or two after she came to the hospital she developed a cord bladder. I know of no more difficult problem with which to be confronted than a patient with a cord bladder, particularly when caused by pernicious anemia.

She had a red, atrophic tongue. This is the typical tongue of pernicious anemia. A test meal showed no free acid. The anemia was a macrocytic anemia. She did not suffer so much from the anemia as from the cord lesion.

Russell L. Haden

She had hyperactive reflexes, marked ankle clonus, bilateral positive Babinski reaction, and impaired vibratory sense. She had all three phases of the disease: the gastrointestinal, as shown by the smooth, atrophic tongue and the achlorhydria; the hematologic, as shown by the evidence of a marked macrocytic anemia; and the neurologic, as shown by the signs which I have just outlined.

She gradually improved with treatment and finally returned to her work. First she got out of bed, then out of the wheelchair, then off her crutches, and finally dispensed with her cane. She now walks perfectly well except for some stiffness. It is our experience that the neurologic manifestations almost never disappear completely but they do lose their clinical or functional significance.

Pernicious anemia is a disease we never cure. We have not cured either one of these patients, but we supply the missing element, the lack of which produced the disease. As long as this element is sufficiently supplied, the disease,

while there, is never active and never means anything to the patient.

Two other patients illustrate some other phases of this disease. The third lady came in because of a sore tongue. About 10 per cent of the 600 patients recently analyzed came in because they had a sore tongue. The tongue will get very sore; the disease is always associated with a clean tongue and a smooth tongue. The smooth tongue is the result of atrophy of the papillae.

The patient had had this sore tongue several years but no diagnosis had been made. In addition to that, she had had paresthesias. She did not know about the anemia. The neurologic manifestations of paresthesias and the sore tongue brought her in.

Again, on examination the only thing we found, besides the tongue, was that her spleen was palpable. I have already said how uncommon that is, but here we have two of five patients who had a palpable spleen. She had a questionable Romberg test; the vibratory sense was lost in her feet. She had a marked disturbance of position sense. The position sense has now returned to normal and her vibratory sense, even down to her toes, is perfectly normal. She had no free hydrochloric acid on a test meal. The blood has now returned to normal and has remained normal after this first period of treatment. Usually about three months is required to bring the blood to normal.

The next patient, a gentleman, came in because he was short of breath. I have not mentioned shortness of breath. That is one of the first things we think of in anemia. He had a very sallow color. It was apparent that he had a marked anemia. There was nothing wrong from the standpoint of his blood pressure or heart to make him dyspneic; it was perfectly apparent that his shortness of breath was due to anemia. His red-cell count was 1,380,000. He had 32 per cent hemoglobin. That is quite low for a man who is working as hard as he had been.

He had big red cells. We measure the red cells from the standpoint of the volume index. This indicates the size of the cell relative to normal rather than in microns. The size of a red cell is very simple to calculate. There is nothing new about it. What the clinician wants to know is the size of the red cell relative to normal. Volume index, which is calculated from the hematocrit reading and an accurate red-cell count, indicates this.

The patient had no free acid. An important thing to be determined from test meals in patients with pernicious anemia is achlorhydria. There also is a very low total acidity which is very important. With an achlorhydria due to chronic nephritis there may be no free acid, but the total acid is usually high. Even when the patient is tested with histamine, no free acid is found in the gastric content in cases of pernicious anemia.

This patient's blood has now returned to normal and has remained so over a period of three years.

There is no reason why these patients should not remain perfectly normal. If they do not, it is either the doctor's or patient's fault, and in my experience, it is usually the doctor's fault.

Each of these four patients has been treated with liver and liver extract. The first patient ate liver for a long time and progressed favorably. She began treatment in 1931, when liver extract was inferior, and for many years she ate liver. The only difficulty encountered was that occasionally when she would discontinue liver she would develop some trouble. What would the trouble be? The very first thing to happen when treatment is not adequate is enlargement of the red cells. This develops even before the hemoglobin decreases. This always means that the patient is not being completely treated.

Folic acid recently has been used for the treatment of macrocytic anemia. This may be the specific principle in liver extract which is responsible for the relief of pernicious anemia. This has not been proved, however.

About three months ago we saw in one day three patients with pernicious anemia who had never been treated. It is often difficult today to

make the diagnosis of pernicious anemia because the patients have usually been given liver extract without an adequate study. The first thing to try is a test meal if the patient has been treated. If acid is present he does not have pernicious anemia. If he has no free hydrochloric acid, pernicious anemia may or may not be present.

These three patients had well-marked pernicious anemia. I treated the first with liver extract by the method we have been using for many years. The second had 10 mg. of folic acid by hypodermic injection; the third had 20 mg. given by the same schedule instead of liver extract. Interestingly enough, these three patients all got exactly the same final result. With folic acid the reticulocyte count does not rise to the level calculated from the use of liver extract, but so far as I can see, the results are exactly the same.

SHOULD we use folic acid? I do not know. It is new. I, for one, shall stick to liver extract until we know more about folic acid and can determine exactly what role it will play. All of us are hoping that folic acid may give a better result; that it may have a greater effect on the neurologic manifestations of pernicious anemia than liver extract has produced. I doubt it because I think the trouble with the management of the neurologic manifestations of pernicious anemia has been that the treatment has not been carried out properly.

It takes about three months for the blood to return to normal. After only two and a half months one patient's count was 4,350,000 and her hemoglobin 81 per cent. She still has a volume index of 1.07. You may say that this doesn't amount to much, but it certainly does. It means that she still is not well hematologically.

How should liver therapy be given? Liver extract parenterally is the treatment of choice. We are all besieged by the detail men with extracts of all sorts of potency. I have in my files the advertisements of all the major pharmaceutical houses, each with a number of extracts. The potency must always be kept in mind.

A unit should be the amount of specific principle needed to supply one person for one day. We have always used an extract containing 15 units per cc., which is the ordinary concentrated preparation. Another manufacturer will have one with 10 units, others with 3 and 5 unit extracts. I don't see any sense in that whatsoever. I see no point in using an extract containing less than 15 units per cc. The material is stored in the body and not rapidly excreted. It is important to select an extract that you know is good, that you can depend upon, and then stick to it.

It is a good investment for the patient to spend the first two weeks of treatment in the hospital. Pernicious anemia is a very serious disease. Before 1926 all patients who had it died. A stay in the hospital emphasizes to the patient the seriousness of the disease. During this two-week period an intramuscular or subcutaneous injection of 15 units of a known potent liver extract is given daily. At the end of this time we start similar injections of the same amount twice weekly for three months. The next three months 15 units are given weekly; the next six months 15 units, twice a month. This covers treatment for the first year. One injection of 15 units is given monthly for the rest of the patient's life. With intercurrent disease, more frequent injections are required.

All of our patients understand before we discharge them that we have not cured their disease; we have simply returned the blood to normal. We emphasize that they have to take specific treatment for the rest of their lives.

The length of time that a patient can go without recurrence of symptoms in the absence of treatment of pernicious anemia is extremely variable. As a rule, the anemia and other symptoms recur in a few months at most. Recently we had a patient return who had had no treatment for five years. After her blood returned to normal, she had discontinued injections. She again had marked anemia, but had gotten along quite well for five years. This is the unusual. To discontinue treatment is dangerous.

What you do with this disease is to supply a deficiency which the patient can never supply himself since there is an unalterable defect in the stomach mucosa. You should use a potent liver extract and, at the beginning of treatment, give it intensively. The treatment must be given for the rest of the patient's life.

This method of treatment, while intensive at the start, requires fewer injections in the long run than the usual method. It is not necessary to give injections frequently after the preliminary period of intensive therapy. I often see patients who have been given injections of liver extract twice weekly. This is not necessary.

I come back to the tongue again because I cannot mention it too often. If a person has a tongue with long papillae and a little coating, it is perfectly normal. There is not one such person in a million with active pernicious anemia. On checking patients, one can often tell their need for liver extract simply by looking at the tongue. A clinician should never overlook the inspection of the tongue.

The blood should be studied regularly. If the patient follows the treatment suggested, the blood will be perfectly normal all the time. I tell our patients that every three to six months they should have a complete blood study because we can quickly tell in the laboratory whether the treatment is sufficient or not.

All pernicious anemias during the active stage are macrocytic. That means the cells are large. A macrocytosis develops long before there is an increase in the color index, which is often emphasized but is dependent on the increase in cell size. To determine the red-cell volume a hematocrit reading is made after centrifuging a fixed amount of blood. The mean cell size is calculated from this simple data. The size of the normal cell is 90 cubic microns and the normal volume index is 1.00. If a person develops pernicious anemia, the red cells get larger.

If liver extract is given to a patient who has a macrocytosis that is caused by the lack of the specific principle supplied by liver, the red-cell size returns to normal.

Iron has exactly the opposite action to that of liver extract. Iron makes the cell larger, not smaller, by filling the cell with hemoglobin. A normal cell with an iron deficiency becomes smaller. The mean volume here is 66 cubic microns, so the volume index is 0.73. With iron, the cell becomes larger and returns to normal.

Is hydrochloric acid given? No. Nobody wants to take hydrochloric acid unless he has to. So far as I can see, it doesn't help a bit in pernicious anemia unless it is indicated for some symptom such as diarrhea.

Should iron be used? No. Iron and liver should rarely be given at the same time except to some person who has both an idiopathic iron deficiency and an idiopathic pernicious anemia.

In conclusion, I wish to emphasize again the marvelous results one gets in the treatment of pernicious anemia by proper diagnosis and treatment. Liver extract is the specific method of treatment which should be used for the present. The place of folic acid in the treatment of this disease is still undetermined.

DIAGNOSTIC CLINIC

Differential Diagnosis of Obstruction at the Bladder Neck

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As a preface to this discussion, I should like to present 3 cases. The first patient, Mr. K., who was eighty years of age, came into the hospital complaining of bladder trouble; he had marked difficulty in passing his water and experienced frequent attacks of complete retention. The symptoms were of several years' duration. The patient had made a practice of catheterizing himself for the attacks of retention. This was sometimes necessary several times during the day or night.

The significant findings were that he was eighty years old; his blood pressure was 265/124; there was marked arteriosclerosis and some cardiac enlargement, but no sign of heart failure. The rectal examination showed a 2+ enlargement of his prostate, which was symmetrical, with the right lobe being more firm than the left.

From the history and the examination it was obvious that the cause of this patient's bladder-neck obstruction was an enlargement of the prostate. He had a resection, which appeared to cure the condition.

The second patient, Mr. J., sixty-one years old, was first seen at the Cleveland Clinic. He had complete urinary retention for four to five days before he came to the hospital. It was necessary for him to be catheterized. For several months he had had symptoms of a developing urinary obstruction, characterized by increased frequency and slowing of the urinary stream. The general physical examination was negative. Rectal examination showed only a grade I enlargement. There was some irregularity of the outlines of the prostate; there were no evidences of bone metastases. This patient had a transurethral resection, and also was given stilbesterol. The condition now appears to be cured.

The third and last patient, Mr. S., reported having the same symptoms as the other two patients. He had a grade III hypertrophy. He had a resection which gave him temporary relief; with a recurrence of his symptoms, it was necessary to do a suprapubic prostatectomy and 335 gm. of tissue were removed.

These three patients had in common symptoms of obstruction at the neck of the bladder. When a male patient comes in who is over fifty-five or sixty years of age and has this group of symptoms, as a rule the diagnosis of prostatic obstruction is made and there is not very much of a problem. However, there are a great many other conditions with respect to obstruction, or symptoms of obstruction, at the bladder neck that require careful study, careful elicitation of the symptoms, and a careful physical examination.

The various lesions that produce symptoms

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of bladder-neck obstruction may occur not only in men of the prostatic age, but also in women and even occasionally in children. Symptoms of obstruction are more common in boys than in girls.

Let us therefore consider the various lesions that may be responsible for bladder-neck obstruction. The organs that may be responsible for this clinical picture are: prostate, prostatic urethra, bladder, ureter, central nervous system, gynecological tract, and rectum.

As will be seen from the following outline many lesions of these organs are capable of producing this picture.

I. Lesions of the prostate
  A. Benign
    1. Lateral lobes
    2. Middle lobes
    3. Bars and contractures
  B. Carcinoma
  C. Calculi
  D. Cysts
  E. Abscess
  F. Sarcoma

II. Lesions of the prostatic urethra
  A. Valves
  B. Hypertrophy of the verumontanum
  C. Impacted stones
    1. Prostate
    2. From above

III. Lesions of the bladder
  A. Stones, large or impacted
  B. Dumb-bell
    1. Intravesical
    2. Intra-urethral
  C. Pedunculated papillomata and pedunculated tumors
    1. Benign
    2. Malignant
  D. Carcinoma
    1. Cavity
    2. Trigone
    3. Neck
  E. Cysts of trigone
  F. Hypertrophy of interureteral ligament

IV. Lesions of ureter
  A. Ureterocele

V. Central nervous system
  A. Cerebrum
  B. Cord
    1. War injuries and other trauma
    2. Tabes
    3. Pernicious anemia
    4. Tumors
    5. Disc operations
    6. Spina bifida
  C. Lesions of nerve supply

VI. Lesions of gynecological tract
  A. Fibroids
  B. Ovarian cysts
  C. Cystocele
  D. Rectocele

VII. Lesions of rectum
  A. Large tumors

The most common lesion of the prostate that produces obstruction is the simple enlargement, the so-called benign hypertrophy. The enlargement may consist of lateral lobes or of a middle lobe, or there may be a combination of both the lateral lobe and middle lobe. The patient with benign prostatic obstruction gen-

erally gives a typical history. The disease process is insidious in its onset; the symptoms are progressive in character; and finally the patient has complete retention. This occurred in the three cases that I discussed previously.

Given a patient sixty years of age or older whose symptoms began four or five years ago and have been progressive, a tentative diagnosis of prostatic enlargement can be made. As a rule, these patients are obliged to void once at night and gradually the patient has to void two, three, four, and sometimes five or six times. Associated with frequency of urination at night are symptoms such as pain and burning, small stream, and sometimes dribbling and hesitation. Interruption of the urinary stream is rare in prostatic hypertrophy except in those cases in which the patient has a pedunculated middle lobe.

When the condition has persisted for a long time, the physical examination may show the presence of a suprapubic tumor due to distention of the bladder. Later in the course of the disease the patient may dribble all of the time because he has a so-called paradoxical incontinence. Rectal examination will show enlargement of the prostate. In most of these cases it is well to determine the amount of residual urine by passing a urethral catheter, which must be done under very strict aseptic and antiseptic precautions.

When the patient has symptoms of bladder-neck obstruction, is of prostatic age, and has a negative rectal examination, it is necessary to remember that the patient's symptoms may be due either to a small pedunculated middle lobe which cannot be palpated through the rectum, or to a median bar, or to a contracture of the internal urethral orifice. At this point in the examination, it is well to bear in mind the possibility that the symptoms are due to the presence of a lesion outside the urinary tract; this situation calls for a careful differential diagnosis in order to determine the cause of the symptoms. Patients who have prostatic symptoms and whose rectal examinations are negative have been designated by the French as cases of prostatism without a prostate.

Carcinoma of the prostate is the next most frequent cause of obstruction in elderly men. It has been estimated that carcinoma is present in about 20 per cent to 22 per cent of all men who consult a doctor for prostatic symptoms. In some patients with carcinoma, the typical history is not present. The patient may have a slight amount of urinary distress, and he presents himself for examination when complete retention has a very sudden onset. It must be remembered that some patients with carcinoma of the prostate may have vague and indefinite pains in the bones and that these symptoms are due to metastatic carcinoma. In an occasional case a very mild injury results in a fracture of the femur, humerus, or ribs, and this may be the first inkling that the patient has trouble with his prostate.

I ONCE saw a patient with no urinary symptoms who was treated a long time for intercostal neuralgia. Autopsy disclosed a small nodule, the size of a large pea, in the center of his prostate. He had many metastatic areas in his bones. It was not a case of pure intercostal neuralgia, but was intercostal neuralgia due to fractured ribs secondary to carcinoma of the prostate. In most cases of carcinoma, the rectal examination shows changes in the prostate. The prostate no longer has its normal consistency; the borders are no longer sharply defined, and the surface may be irregular and nodular. In cases of late carcinoma the lesion extends beyond the capsule and may infiltrate the seminal vesicles.

Patients with calculi in the prostate have symptoms of obstruction. There are two types of patients with prostatic calculi. In the first group are the patients with small calculi that are discovered on routine roentgen-ray examination. These generally occur in men with chronic prostatitis. They have practically no significance because they produce no symptoms.

To the second group belongs the patient who has a large stone in his prostate and has all the symptoms and signs of obstruction, namely, frequency, painful urination, and often residual

urination with superimposed infection. When the stone is large, it can be felt through the rectum as a large nodular area. When the stones are smaller and multiple, one can elicit a feeling of crepitation. The roentgen ray, of course, shows the presence of these stones. It might also be mentioned that in patients with benign hypertrophy small stones may be present; they, of course, do not produce symptoms that bring the patient to the doctor. The symptoms are due to the hypertrophy itself.

Let us also consider at this point the patient who has a stone in his prostatic urethra. In some of these patients one may obtain a history of a renal colic, either recent or remote. The patient during his attack of renal colic may pass the stone into his bladder and from the bladder into his prostatic urethra, where the stone may become lodged and produce all symptoms and signs of obstruction. In an occasional case the stone in the prostate itself may rupture or may perforate the prostate, find its way into the prostatic urethra, and become lodged. The patient then has symptoms of obstruction.

Prostatic cysts are very uncommon. They are generally located around the bladder neck, and in this particular place they produce symptoms of obstruction.

Abscess of the prostate is an acute affair. It usually occurs in young men. They may or may not have had a recent acute urethritis. On the other hand it is not at all uncommon to see patients with a metastatic abscess of the prostate. Here the history is most important and any of the following conditions may have preceded the abscess: a history of acute cold, an attack of influenza, an attack of tonsillitis, furunculosis, a carbuncle, a patch of eczema, or an osteomyelitis. In some patients an acute abscess of the prostate follows urethral instrumentation. The patient with an abscess is an acutely ill patient. The rectal examination shows a large, boggy swelling of one lobe of the prostate, usually associated with fluctuation.

Bilateral abscess is rare. This condition should offer no particular problems in the differential diagnosis.

Sarcoma of the prostate is very rare and generally occurs in young adults, though this condition has been seen in children. When you are consulted by children or young adults with a history of a rather rapid development of urinary obstruction, showing first great difficulty in urination and finally complete retention, it is always well to consider the possibility of a sarcoma of the prostate. The rectal examination is very often of great value since a large prostate which may completely fill the pelvis may be present. Upon making a rectal examination, one obtains a peculiar sensation with the examining finger. It is not the feeling of the benign hypertrophy, nor is it the feeling of the carcinoma of the prostate. Once you have obtained this impression on rectal examination you will never forget it. It is quite characteristic.

LESIONS of the prostatic urethra, exclusive of the lesions just mentioned, are relatively uncommon.

Valves of the prostatic urethra and hypertrophy of the verumontanum produce severe symptoms of obstruction. These lesions occur in young children from the age of two, three, or four up to ten or twelve. As a rule, when the patient is first seen, the history shows symptoms of long duration, such as difficulty, straining, and a very small stream; also it takes a long time for the patient to empty his bladder. When dribbling is present, it is nearly always due to overflow incontinence, the so-called paradoxical incontinence. Because of this incontinence the true condition is not recognized, and these patients are treated as cases of enuresis. If, with this more or less typical symptom-complex, the examination shows the presence of a suprapubic tumor, the diagnosis is self-evident.

I have already discussed stones impacted in the prostatic urethra which may have their origin in the kidney or in the bladder and may become lodged in the prostatic urethra. Although lesions of the bladder rarely produce obstruction to urination, certain lesions result

in symptoms of obstruction. Bladder stones may become impacted in the vesical orifice. A large stone may interfere with urination because of its proximity to the bladder-neck and hence produce symptoms of obstruction. Dumbbell-shaped stones with one part in the bladder and the other part in the prostatic urethra produce very severe symptoms of obstruction.

Certain bladder tumors produce obstruction and difficulty in urination, such as pedunculated papillomata fibromata, and muscular tumors. In an occasional case a long pedunculated polyp may produce symptoms of obstruction. In these cases it is possible to obtain a history of interruption of the urinary stream.

Carcinoma of the bladder may involve the internal ureteral orifice and produce symptoms of urinary obstruction. A tumor with its origin in the trigone or a cyst of the trigone may produce obstruction. Some of these pedunculated tumors may have their origin in the dome of the bladder, and a large tumor impedes or obstructs the bladder-neck so that the patient has great difficulty in urination and in some instances may even develop complete retention.

Cysts of the trigone are rare and are mentioned only to call attention to the fact such a lesion does occur and that in an occasional case it may produce symptoms of bladder-neck obstruction.

Hypertrophy of the interureteral ligament may produce obstruction. This is generally due to obstruction at the neck by changes in the prostate. Unless this condition is recognized, the patient may continue to have symptoms after the prostatectomy.

Although lesions of the ureter producing obstruction to urination are rare, they do occur, especially in children. They occur with sufficient frequency to bear them in mind. I refer, of course, to so-called cystic dilatation of the vesical end of the ureter, sometimes called ureterocele. I have seen cases in children in which the ureterocele completely filled the bladder, resulting in complete retention. As a result of the tenesmus, the ureterocele may protrude from the external urethral orifice in girls.

Lesions of the central nervous system may produce obstruction to urination. The possibility of their occurrence must always be considered. Errors in diagnosis may easily occur unless careful search is made. Patients with tabes dorsalis have had bladder operations. Some of the patients belonging to this group, because of their bladder symptoms, have had long courses of local treatment with no relief of their symptoms. The various types of lesions of the central nervous system are too numerous to mention. I have already called attention to the fact that tabes dorsalis may be overlooked. The patient with pernicious anemia may have degeneration in the spinal cord with resulting urinary symptoms.

Spina bifida, tumors of the spinal cord, extrapyramidal tract lesions, multiple sclerosis, myelitis, and spinal cord injuries may also be responsible for the symptoms of urinary distress. Because of the present-day wave of enthusiasm for disc operations, may I point out that I have seen three patients who developed complete retention following this operation. The management of this type of patient presents many interesting problems, particularly the so-called spinal cord bladder, the result of war injury.

I would like to point out that the patient with tabes may also have a bilateral enlargement of the prostate. Formerly patients with this combination were advised not to have a prostatectomy because the prostatectomy would be followed by incontinence. This was unfortunate. I have performed suprapubic prostatectomy on 6 to 8 tabetics, and they did not develop incontinence. At the present time a patient with this combination can be relieved by transurethral resection.

Lesions of the gynecological tract producing urinary symptoms, especially those of obstruction, are relatively common. As a matter of fact, it is because of the urinary difficulty that the patient first consults the urologist. It therefore becomes increasingly important that women having symptoms of urinary obstruc-

tion undergo a careful urological examination as well as a thorough gynecological examination. In my experience it is not at all infrequent to have a patient consult me for symptoms of bladder-neck obstruction when the cause of the symptoms may be rather a large cystocele and rectocele.

Patients with large fibroids impinging on the bladder often have great difficulty in urinating. Certain types of small fibroids, depending upon their direction of growth, may likewise cause bladder-neck obstruction. Carcinoma of the uterus and large ovarian cysts may also be responsible for symptoms of bladder-neck obstruction.

Lesions of the rectum producing this picture are uncommon. However, large benign and malignant lesions of the rectum and occasionally a large diverticulitis of the bowel bring the patient to the doctor because of symptoms of obstruction.

TREATMENT

TREATMENT of bladderneck obstruction consists primarily of diagnosis. It must concern itself with determining the cause of the symptoms and the location of the underlying pathology. It is perfectly obvious that the institution of treatment under any other premise gets one nowhere. It is a waste of both doctor's and patient's time to institute local treatment to the bladder when the primary pathology is due to a marked cystocele or a large fibroid. It is equally fallacious to treat with bladder instillations the patient who has bladder symptoms due to spinal cord changes arising from pernicious anemia. On the other hand, a patient may have two lesions producing symptoms of bladder-neck obstruction, namely tabes dorsalis and prostatic enlargement. This patient should have a transurethral resection just as though he had no tabes. The patient with tabes can now be relieved of his difficulty, frequency, residual urine, and infection by means of a transurethral resection.

The patient with benign prostatic obstruction is treated by means of transurethral resection. The number of patients who today are subjected to suprapubic or perineal prostatectomy is very small. More and more patients are treated by transurethral resection because the mortality rate is lower, the stay in the hospital is shorter, and complications occur less frequently with resection than with suprapubic prostatectomy. In an occasional case, when the prostate is very large, it may be necessary to perform a second resection. When one cannot introduce the resectoscope, it may be necessary to proceed with a suprapubic prostatectomy. One of the patients I discussed previously had a resection with temporary relief. Because the symptoms returned and because of the size of the prostate, a suprapubic prostatectomy was deemed advisable.

A patient with stricture of the urethra and prostatic enlargement should have the benefit of urethral dilatation before proceeding with the resection. In some instances dilatation of the stricture is all that is needed.

Patients with carcinoma can be treated with resection to relieve the obstruction. The advisability of this depends on the severity of the symptoms, the amount of residual urine, and the presence or absence of infection. After resection these patients should be given stilbesterol by mouth. If the symptoms recur, they may require a second resection. Castration for carcinoma of the prostate has lost its popularity and is on the wane.

Radical operation—that is, complete prostatectomy, seminal vesiculectomy, and removal of the bladder-neck—has its advocates. The drawback to this treatment is that many of these patients come in late in the course of the disease, when the carcinoma has already spread beyond the confines of the capsule of the prostate.

Prostatic calculi may be treated by perineal prostatotomy, or, if they are large or deep-seated, by transurethral resection. In most cases where operation was indicated I performed transurethral resections.

Abscess of the prostate should be treated by perineal prostatotomy. Prostatic cysts can be destroyed with the high-frequency current.

DIAGNOSTIC CLINIC

Uterine Fibroids

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I AM TAKING the subject of fibroids because fibroids are so exceedingly common. Also, they may appeal to many of you as one of the major sources of income to the profession, unjustifiably in many cases, and that is what I want to stress.

Fibroids are perhaps the commonest of major tumors. Graves makes the statement that 40 per cent of all women will have fibroids during their lifetime and that practically all single women of middle age may have them. Cullen, on the other hand, in investigating the records at Hopkins Hospital, said that of all the women who had come to autopsy over 20 years of age, 20 per cent showed fibroids. This figure is rather unfair because we don't usually see fibroids in women before the age of 30; so many of those women who were autopsied between 20 and 30 who showed no fibroids probably would have developed them with age.

Fibroids are more common in the nulliparous than in the parous woman. It may be that the fibroid has caused the sterility. On the other hand, some wag has said that it is simply frustration on the part of the womb, that the uterus says to itself, "Hang it all, if I can't make a baby I'll do the next best thing, I'll grow a tumor."

The colored race is particularly susceptible to fibroids, and in our clinic we assume that any middle-aged negress who comes in, whatever else she may have in the way of pus-tubes or tubal pregnancy, at least will probably have a fibroid.

Fibroids always begin as small nodules, single or multiple, in the wall of the uterus. They are composed of the same elements as the uterus, namely, muscle and fibrous tissue, and are definitely demarcated from the adjacent myometrium. The fibroid is thus analogous to a lipoma in adipose tissue. Why lipomas become discrete and more or less encapsulated we do not know. We do not know the real cause of the fibroid; nothing has ever been adduced to explain it.

Fibroid tumors may vary from microscopic to very large in size. Cullen reported one of 89 pounds, which was the largest reported up to that date. They are practically always in the corpus of the uterus, very rarely in the cervix. If they are in the cervix, they are usually small but are apt to prove more complicated at operation.

These intramural tumors do not remain in the wall of the uterus. They tend to migrate. One reason may be that they grow toward an area of less resistance, either toward the peritoneal surface or into the cavity of the uterus. I think a very important factor in migration is the rhythmic contractions of the uterus, which tend to squeeze the nodules either internally or externally. We know that the uterus is rhythmically contracting all the time. These contractions become particularly increased in

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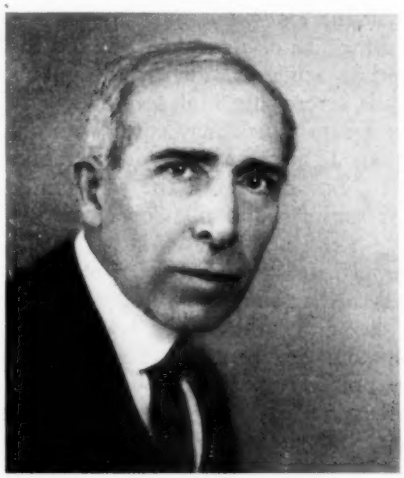


William H. Weir

dysmenorrhea. Labor pains are simply exaggerations of them.

These contractions tend to squeeze the nodule either internally or externally, producing either subperitoneal or submucous fibroids. By far the least troublesome is the subperitoneal nodule, because it will practically never cause bleeding. When the tumor approaches the cavity of the uterus it usually leads to a hypertrophy of the mucosa, and bleeding comes from the mucosa, not from the tumor. It may come from the tumor in the case of necrosis of a submucous pedunculated fibroid, but is nearly always endometrial.

As the tumor is expressed from the wall of the womb into the peritoneal cavity it forms a pedicle. This pedicle may become narrower from the contractions so that the circulation is apt to be more or less cut off, and there may be a necrosis of the subperitoneal nodule. There is nearly always what is really a necrosis, hyaline degeneration, in a fibroid of any size. The whole nodule may be visibly degenerated, or it may be microscopic. When the circulation through the pedicle becomes impaired, there may be adhesions formed to the omentum. New vessels will grow from the omentum into the nodule and ultimately nourish it. The pedicle may become completely severed, resulting in a "parasitic" fibroid, a fibroid that began in the wall of the womb and ended by having no anatomic connection with it at all.

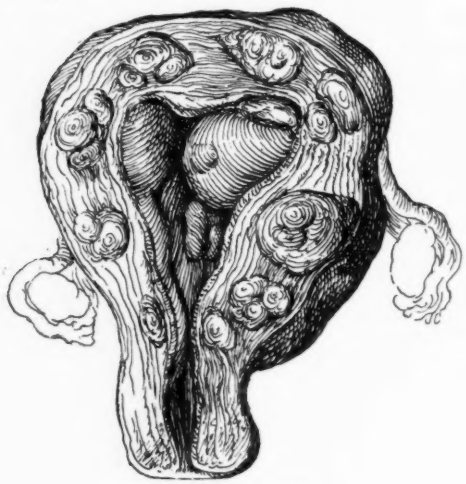
Similarly, a tumor in the cavity of the womb becomes pedunculated, really forming a foreign body inside the uterus; the contractions are increased and it is expelled as any foreign body might be. The pedicle elongates, becoming longer and longer; the tumor dilates the cervix, enters the vagina, which may be greatly distended by the tumor. Finally the pedicle may part and the tumor be expelled, resulting in what one might call a spontaneous cure of a fibroid.

An intraligamentary fibroid is one that has grown outward from the uterus and happened to develop between the walls of the broad ligament. It is in no way different from any other except in the operative difficulties which it may offer. Like a parovarian cyst, it may lead to tremendous elongation of the tube, but the main danger is from distorting the relation of the ureters, which may be damaged in operation.

There is one other type of tumor closely allied to the ordinary fibroid, and that is the adenomyoma, which differs in the fact that scattered through it are areas of endometrium. It is more of an endometriosis than a true fibroid. It offers difficulties in myomectomy because it is not well defined. Usually fibroid nodules are sharply defined, so that they can be easily shelled out, but the adenomyoma shows no definite capsule and is much more difficult to handle.

What happens to these fibroids? As a rule they grow slowly. Sometimes they grow rapidly, which leads to the fear that they may be malignant. They may be subject to rapid increase of size as a result of sudden edema, particularly generalized edema, which may subside later. Not infrequently in the case of medium-sized fibroids, one may find the fibroid slightly increased in size before the period, and it may regress afterward.

These tumors may undergo slow growth or remain stationary until the menopause, when they behave exactly as the rest of the uterus does—they atrophy. It doesn't make any difference whether the menopause comes on naturally or is induced by radiation or surgery. In the early days of surgery, hysterectomy was regarded as a very dangerous operation but



Multiple Fibroids

ovariotomy was much simpler, so they simply removed the ovaries.

These tumors tend to degenerate. They have a very poor blood supply. The common degeneration is the so-called hyaline degeneration, which is really a necrosis. The whole tumor loses its vitality, but fortunately the presence of the dead tissue rarely does any harm. As a consequence of the degeneration there may be more or less calcification, so that sometimes a large fibroid may be turned into a stony mass which cannot be cut with a knife but may be divided with a saw much as you would soft marble.

One may find also myxomatous degeneration. This soft dead tissue may liquefy and form large cysts in the substance of the tumor.

There is a particular degeneration for which one must be on the lookout, the so-called acute red degeneration, which is particularly prone to occur in pregnancy. It is an acute process. One patient I saw not long ago had a large fibroid the size of a coconut. She suddenly developed an acute abdomen with rigid abdominal walls, severe pain, high fever, leukocytosis—all the things which may occur with an acute infection. I suspected red degeneration. We waited a few days until the acuteness of the process subsided and then operated.

THE DEGENERATION we fear is of course, sarcoma. Textbooks very often stress this a great deal and I think very unwisely, because sarcomatous degeneration rarely occurs. The microscopic picture in many of these fibroids is misleading, and one cannot depend upon every pathologist's report. A rapidly growing, cellular fibroid may give exactly the picture of a sarcoma. More important is the clinical record of the case, because if you have a sarcoma of the uterus you are rarely going to get rid of it by operation. Very early there will be multiple adenomyoma, which differs in the fact that metastases, as the clinical records usually reveal.

I looked over our records at the University Hospitals and found that in the last twenty years there were 328 cases of malignancy involving the corpus of the uterus. The vast majority of those were adenocarcinoma originating in the endometrium. Of these 328 cases, there were only 7 that showed any sarcomatous change. Five of these 7 happened to have fibroids, but in no one of those 5 was there any evidence that the sarcoma had started in the fibroid.

Opinions vary as to whether fibroids predispose to the development of adenocarcinoma, which of course must originate within the endometrium, since there are no epithelial elements in the fibroid. Of course, if 40 per cent of women have fibroids, you are going to find them in a great many adenocarcinoma cases, but that is not proof that the fibroid had anything whatsoever to do with the development of the carcinoma.

What symptoms do patients with fibroids have? Often they have none whatever. An instance is the case of a young woman who went

to join a gymnasium class, and the doctor looked her over lest she might have a heart lesion. He referred her to me because she had a tumor. The tumor extended up below the costal margin. It happened to be flat, so the slightly enlarged abdomen was perfectly smooth, and she didn't even know that she had a lump there. I went over her with a fine-toothed comb and could find no menstrual disturbance, no pain, no disability whatever.

Another patient said, "Doctor, there is nothing wrong with me except that my clothes won't hang straight." When she stood up, she looked as if she were going to have triplets the next minute, which was very embarrassing for an unmarried school teacher. In that case, except for a huge fibroid, the only abnormality I could find on examination was slight edema of the ankles.

BLEEDING is the common and outstanding symptom of fibroids. It comes from the endometrium, which is usually hypertrophied. It may be far more dangerous and profuse in the case of a submucous tumor, and if such a tumor becomes ulcerated or degenerated, the bleeding may come from the tumor itself. Nearly always, however, the hemorrhage is endometrial.

The bleeding recurs with every period; the woman may lose more blood at each menstruation than she can quite make up during the interval; there is a gradual increase in the anemia at every period, but perhaps not so rapidly as to attract her attention.

In addition to bleeding she may have pressure symptoms, which may be simply a dragging-down due to the weight of the tumor, such as occurs with an ordinary uterus if the perineal supports are inadequate. Undue strain on the supporting ligaments of the uterus may lead to reflex nervous symptoms or the tumor may give rise to pressure, causing pain down the legs, and backache. Urinary symptoms may develop from crowding the bladder, but are often due to the fact that these large tumors nearly always cause some degree of hydronephrosis by pressure on the ureter, and the bladder symptoms are reflex from that.

Large tumors may cause edema of the ankles and varicosities, just as will the pregnant womb. They may produce a leukorrhea because the endometrium is hypertrophied and there is more secretion, usually a thin, watery fluid, but in the case of a necrotic submucous fibroid there is a foul, ill-smelling discharge which may closely resemble that of carcinoma.

Sometimes there may be really acute pain due to red degeneration or to torsion of a pedunculated tumor or from tension on bowel adhesions or other adhesions internally. At times an infection of a degenerated fibroid may occur when the tumor is adherent to the bowel, although in a necrotic tumor, otherwise aseptic, the germs may reach it through the blood stream.

The diagnosis of fibroids is usually easy in most cases, though sometimes it may be exceedingly difficult. The thing about which we have to be very careful is pregnancy, especially where the tumor causes a symmetrical enlargement. Frequently a fibroid and also pregnancy are encountered. If the tumor is large and very nodular, anybody can feel it, although the same nodular feeling may be presented by a multilocular ovarian cystoma.

In cases that have been referred to me by other doctors I have found that a very common error is to mistake a retroverted uterus lying back in the cul-de-sac and perhaps somewhat hypertrophied, for a fibroid. I have had many of those come to me diagnosed as fibroids when they were simply retroversions. Any inflammatory mass in the pelvis may resemble a fibroid and cause a mistake in diagnosis. No one can feel the very small fibroids, and even when they get larger, the diagnosis may be very difficult.

In one very interesting case of bleeding from the bowel, I did an exploratory, and there was a fibroid about an inch and a half in diameter so densely adherent to the right cornu of the uterus that it had to be separated by sharp dissection. It was not a uterine fibroid. It was a

fibroid of the terminal ileum, which accounted for the bowel bleeding and which, in some inexplicable way, had become adherent to the uterus.

Occasionally you may examine a slightly symmetrically enlarged uterus and fail to diagnose a fibroid, and at a later visit there, in the cervix or actually lying in the vagina, is a submucous fibroid which has delivered itself and is now perfectly obvious.

The treatment is the important thing. In most of these cases a "policy of masterly inactivity" is all that is necessary. The small or medium-sized tumors may not be causing symptoms, and they may have been discovered in a routine examination, not infrequently because the patient comes in for sterility, and the examination reveals the tumor.

A favorite question of mine in examining students is what they would advise if a young woman 30 years old comes in wanting a premarital examination and some contraceptive advice and they find a fibroid tumor of the uterus a couple of inches in diameter but causing no symptoms. Of course many of them want to operate. The answer I want is to do nothing but to advise that young woman not to use any contraceptive measures and to try to become pregnant just as quickly as she can. In a few years the tumor may have grown or other complications may have developed so that she cannot then become pregnant.

Then comes the palliative treatment. How are you going to deal with the bleeding? The first thing you use, provided the tumor is of moderate size and is not causing too much trouble otherwise, is drugs. For this purpose, ergot or ergotrates are often used. I depend largely upon fluid extract of Hydrastis in 15 drop doses, or stypticin, which is a closely allied drug. In recent years, testosterone has been found very efficient in these uterine hemorrhages, giving about 25 mg. hypodermically every day or so, but not using more than about 300 mg. in any one month, for fear of producing masculinizing symptoms.

If the medicine does not control the bleeding, the next step naturally would be a curettage. In a great many cases we want to do the curettage for other reasons, too. These tumors develop in the cancerous age and the woman may have a fibroid, but she may also have a cancer, and we want to be sure, if we are going to treat the case palliatively, that there is no cancer.

The curettage is often difficult because the tumor may have enlarged the cavity and it may be so irregular from projecting fibroids that you cannot adequately curette the whole surface.

I have curetted a case and had to take the uterus out soon afterward, finding a big polyp that had evidently been pushed aside by my curette and not removed. I would strongly advise using a ring forceps. Put the ring forceps up into the cavity, open and then close it, and you may grab a pedunculated fibroid or mucous polyp which you can twist out with perfect safety.

You must correct the anemia, either by iron or liver, et cetera, and not infrequently you may even have to give a transfusion.

We radiated one patient who should have been operated upon but who refused operation, and while we were waiting for the effect of the radiation she had another period and almost bled to death, needing repeated transfusions until the radiation became effective.

For the dragging and pain you can do certain things. I have found great relief comes in some cases from simply putting in a pessary, which will take the weight off the ligaments. If there is a retroversion and you can correct that, it may help a good deal. Particularly in the case of tumors that are incarcerated in the pelvis, you may be able to work them up above the brim of the pelvis where there is more room and give the patient considerable relief.

The palliative treatment is particularly indicated in younger women who have not had but want children and in whom you do not wish to destroy the child-bearing function. There are other women who flatly refuse to

have anything done, either radiation or operation, and you have to do the best you can under those circumstances.

Next would be conservative surgery. You want to preserve the child-bearing function. For this purpose we do a myomectomy. I do not like doing myomectomies because if you do it to promote pregnancy, the patient, having had an abdominal operation, fully expects to become pregnant. You cannot guarantee it, because some other factor may have been preventing the pregnancy. However, if the fibroid is bleeding and is liable to interfere with pregnancy, we do a myomectomy. I always warn them very carefully, "We may take out every last fibroid we may find and in a year or two you may have a lot of others."

RECENTLY I had two patients in one room, side by side, with large bleeding fibroids requiring hysterectomy. It so happened that exactly 13 years ago I had operated on both of them, doing a conservative myomectomy. In the interval one had had a baby. You must always warn your patient that if you do a myomectomy they may develop other fibroids, which may have been present at the time of operation but were too small to be recognized.

If myomectomy is not feasible, you have to do something more radical. The simplest radical procedure—and I mean radical, because it destroys the child-bearing function—is radiation, which may be done by inserting radium in the cavity of the womb. This is often awkward because the cavity may be large and irregular. Practically, I find that radiation by deep x-ray therapy is just as efficient and has many advantages. It is very simple, much less expensive, absolutely safe, or as nearly safe as can be, and does not hospitalize the patient; the patient need not give up her job, but can go right on with her work. The treatment is very effective.

Radiation is not usually advised in large tumors. They should be removed because of the danger of hydronephrosis from pressure on the ureter. Any large tumor ought to come out, but a tumor not over the size of a three-and-a-half-month pregnancy can be very adequately radiated. Radiation does not remove the tumor, it is still there, but it becomes much smaller and practically never causes any subsequent trouble.

I do not see any reason why inducing the menopause is going to do the woman any harm. She has to go through it anyway; she cannot avoid it. I do not think a menopause induced by radiation is in any way worse than the natural one.

Next is radical operation, and I believe in a *radical* operation. I take out the whole womb, cervix and all. The cervix is a great troublemaker. You cannot tell anything about the cervix from the look of it; it may be chronically inflamed and yet look perfectly normal. I have no sympathy whatsoever with the man who does a supravaginal hysterectomy and leaves a small amount of endometrium so that the woman will continue menstruating for her own satisfaction. I never yet saw a woman who, if you explained things to her satisfactorily, was not tickled to death to get rid of this messy, unnecessary function of bleeding every month. You have to explain why the menses are not necessary to her health.

In dealing with fibroid tumors therefore, the majority of small- or moderate-sized tumors which are causing no symptoms need no particular attention other than keeping them under supervision until after the menopause. If symptoms such as simple bleeding occur, medication may be all that is necessary or a curetting may also be indicated. In women desiring children, conservative treatment should be used if possible and this may necessitate a myomectomy. If the symptoms cannot be controlled by such measures and the tumor is not too large, radiation may be required. Many small- or moderate-sized tumors that might easily be radiated had better be removed by operation if there are other reasons for an operation, such as a relaxed vaginal outlet or other birth traumata. The large fibroids should always be removed on account of the danger of hydronephrosis.

EDITORIALS

MEDICAL EDUCATION

The experience gained in World War II has emphasized the importance of preparedness, offensive and defensive, to meet many emergencies. Among the lessons which we, as a profession, have learned is the importance of adequate medical care for those in the armed services as well as for industry, education and civilian needs. Experience thus obtained has pointed out the need of establishing necessary facilities for continuing medical education of students and internes, and also for providing educational programs for training of graduates in medicine and the establishment of short postgraduate courses.

Already medical schools and hospitals have received more requests for training in undergraduate and graduate medical education than their limited facilities can accommodate. Many of these requests come from veterans whose medical training was interrupted because of military service and every effort is being made to supply these demands. The type of training most desired is being provided through the facilities of medical schools and hospitals and by the institution of short intensive courses for postgraduate instruction given in all parts of the United States for those who are particularly interested in general practice or in the medical specialties. The Surgeons General of the Army and Navy are organizing teaching courses to be given in certain of their respective hospitals for the training of recent graduates in the general practice of medicine and in some of the specialties.

Postgraduate courses, even though of short duration, are most valuable for the physician who can only afford to be away from his practice a short time. With such instruction now available and being utilized by so many physicians the type of medical practice offered to civilian communities and to industry improves constantly. In all sections of the country there are available other opportunities for refresher courses which are of value to the physician already established in practice. Such training is provided on a small scale by many of the county medical societies, on a larger scale by state medical associations, and in particular by the national medical societies, where meetings are devoted to clinics, demonstrations, lectures, round table discussions, scientific and commercial exhibits.

POSTGRADUATE MEDICINE

Official Journal of the Interstate Postgraduate Medical Association

Editor in Chief — CHARLES W. MAYO
Managing Editor — ARTHUR G. SULLIVAN
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The great contributions to the advancement of medical education and practice, afforded by the unparalleled opportunities for the study and treatment of such a variety of diseases and conditions, and in such large numbers, encountered in World War II by physicians in the military service, has created a great desire on the part of many to seek more knowledge of these diseases and conditions, particularly among the younger members of the profession. All of this is most encouraging and as educators we should assume this responsibility and make every facility available for their further training. Such would include ample provision for research and investigation in all branches of medicine as well as instruction which is given in medical schools, hospitals and medical societies. The rapid advancement in medicine must be maintained and augmented in every possible way. The adoption of such a program envisions the regaining of much progress which was temporarily delayed because of the war. Already we are happy to see greater interest manifested in medical training and education.

J. E. P.

BASIC CONCEPTS OF RH BLOOD GROUPINGS

WITHIN the last few years many technical articles have appeared dealing with the Rh factor. The majority, concerned with intricacies of current research, are not readily understood. Yet knowledge of basic concepts of Rh blood grouping is of prime importance not only to specialists in medicine, surgery, pediatrics, and obstetrics, but also to the doctor in general practice.

At the present time most physicians are familiar with the human blood groups of Landsteiner, determined by the two antigens, A and B, which may be contained in red cells of various individuals. Corresponding with these antigens are serum antibodies which appear in a reciprocal relationship. A person whose red cells contain antigen A would naturally have antibody B in his serum and a person whose red cells contain antigen B would have antibody A in his serum.

The base for the blood groupings as given by Landsteiner are: Group O—no antigens in the red cells but antibodies A and B in the serum; Group A—antigen A in the red cells, antibody B in the serum; Group B—antigen B in the red cells, antibody A in the serum; Group AB—both A and B antigens in the red cells, no antibodies in the serum. There are natural or normal antibodies in the sera of various individuals. Because of this it is necessary to know the group of donor and recipient before a transfusion can safely be given.

These blood groups apparently are inherited directly. A child cannot have antigen A in his blood unless the blood of one of the parents contains antigen A. Similarly, antigen B appears in the child only when the blood of one of the parents contains antigen B. Antigen A may be divided into three subgroups, A_1, A_2, and A_3.

Subsequently Landsteiner and Levine found the antigens M and N in human red cells. Every individual has at least one and sometimes both of these antigens, but no one has been found who lacks both antigens. These factors are dominant, as are A and B, and do not appear in a child's blood unless present in the blood of at least one parent. There are no naturally occurring antibodies to correspond with M and N antigens. These antigens are very weakly antigenic to humans, and, for purposes of transfusion, may be disregarded. Like antigen A, antigen N was later subdivided into two parts, N_1 and N_2, making five MN blood groups: M, N_1, N_2, MN_1, MN_2.

Another antigen, P, subdivided into P_1 and P_2, was found which is independent of M and N but genetically follows the same rules. This factor is not usually considered because potent sera for testing are difficult to obtain.

Water-soluble A and B antigens were found in some individuals, in tears, urine, milk, and other body fluids. Alcohol-soluble antigens are restricted to the blood and tissue cells. The former individuals are called secretors and the latter non-secretors (S+ and S—). The pres-

ence or absence of the secretory factor may have some bearing on the low incidence of erythroblastosis due to AB incompatibility of mother and child.

In 1940 Landsteiner and Weiner discovered the Rh factor, so named because the antibody was first obtained by injecting blood from the macacus rhesus monkey into rabbits. When this antibody was tested against human blood, the cells of 85 per cent of Caucasian individuals were agglutinated. In other words, 85 per cent of human beings had the Rh antibody in the blood, and 15 per cent did not. The Rh factor is dominant and never appears in a child's blood unless present in the blood of at least one parent. The Rh factor is like the M and N factors and unlike the A and B factors in that no natural Rh antibodies occur in sera. Unlike M and N factors, however, the Rh factor is highly antigenic to human beings, although there are gradations within this antigenicity.

The Rh blood group is of the utmost importance with respect to transfusion reactions. The first transfusion of an Rh-negative individual with Rh-positive blood would produce no reaction since the patient had not as yet been immunized. Repeated transfusions would most certainly produce untoward reactions, provided enough time had elapsed for development of anti-Rh antibodies. Therefore no Rh-negative female should ever receive Rh-positive blood.

At present, determination of Rh positiveness or negativeness will solve most intragroup transfusion problems. However, two other Rh antisera have been prepared, called anti-Rh′ which gives 70 per cent positive reactions and anti-Rh″ which gives 30 per cent positive reactions. The original anti-Rh antiserum has been designated as anti-Rh_o serum since it is the most important. Because every person is either Rh_o positive or negative and because there are other less potent antigens in the Rh series, a double scheme of four types can be set up. The table following, taken from Weiner, now becomes as important as Landsteiner's familiar AB table. An understanding of this table gives us the key to most Rh problems.

Since incompatibility of Rh blood groups between an Rh-negative mother and an Rh-positive fetus is the cause of the majority of instances of erythroblastosis fetalis, it is necessary to understand their heredity. The Rh_o factor is transmitted as a simple Mendelian dominant by a pair of allelic genes, Rh(dominant) and rh(recessive). An Rh-negative individual would necessarily be homozygous (rhrh) while an Rh positive individual could be homozygous (RhRh) or heterozygous (Rhrh). If both parents are Rh negative, all the children must be Rh negative. If one parent is Rh positive and one Rh negative, either all the children will be Rh positive (when the Rh positive parent is RhRh) or half Rh positive and half Rh negative (when the Rh positive parent is Rhrh). When both parents are Rh positive, all the children will be Rh positive unless both parents are heterozygous (Rhrh) in which case three-fourths will be Rh positive and one-fourth Rh negative.

SCHEME OF THE EIGHT RH BLOOD TYPES

Designation of Types	Reaction with Antiserum		
	Rh′	Rh″	Rh_o
CLINICALLY RH-NEGATIVE INDIVIDUALS (15%)			
rh	−	−	−
Rh′	+	−	−
Rh″	−	+	−
Rh′ Rh″	+	+	−
CLINICALLY RH-POSITIVE INDIVIDUALS (85%)			
Rh_o	−	−	+
Rh_1 (Rh_o′)	+	−	+
Rh_2 (Rh_o″)	−	+	+
Rh_1 Rh_2 (Rh_o′ Rh_o″)	+	+	+

A. S. Weiner. Am. J. Clinical Path. 16:477, 1946.

This scheme is important in discussing with parents who have had one erythroblastotic child, the advisability of future pregnancies. If the father is heterozygous Rh positive, half of his potential children would be Rh negative; thus there is a 50 per cent possibility of obtaining a normal infant. The exact grouping and subgrouping of the parents must be done in a laboratory equipped to carry out such procedures.

Certain incompatibilities of the blood groups

result in a disease in infants known as erythroblastosis fetalis. In order to understand the mechanism of this disease knowledge of the nature of antibody formation in the mother is necessary. For sensitivity to Rh, A, B, or any other factor to develop, the person must first be exposed to the antigen in question. Since erythroblastosis rarely occurs during a first pregnancy, the antigenic cells of the infant presumably enter the maternal circulation during labor and thus may sensitize the mother for any further pregnancy.

Individuals sensitized to agglutinogens such as Rh may form two sets of antibodies, namely agglutinins and/or blocking antibodies or glutinins. According to Weiner the Rh agglutinins like the iso-agglutinins anti-A and anti-B are large molecules and do not pass the placenta readily while the smaller glutinins may pass through. The reaction of the agglutinins on the infant's circulation is clumping while that of the glutinins is usually hemolysis. The clinical manifestations of erythroblastosis fetalis depend upon the type of antibody present in the maternal serum.

Weiner suggests that icterus gravis neonatorum results when maternal Rh agglutinins are milked into the infant's circulation during labor, giving rise to the formation of agglutination thrombi in capillaries and venules of organs where the circulation is slow. The severe jaundice is due to liver damage. Occasionally this syndrome is due to maternal glutinins in the child's blood concomitantly with dehydration of the infant. Other instances may result from AB sensitization.

Rh glutinins, presumably comprised of smaller molecules than Rh agglutinins, more readily traverse the placenta into the fetal circulation during pregnancy and are adsorbed onto the surface of the fetal red blood cells.

The "coated" erythrocytes break down more rapidly than normal erythrocytes in the circulation, giving rise to a gradually progressive anemia terminating eventually with a hydropic stillbirth. The severity of the disease is usually correlated with maternal antibody titer and in milder cases the infant is born alive and can be saved by proper transfusion therapy with Rh-negative blood. Atypical cases may be caused by the presence of small amounts of the maternal Rh agglutinins resulting in hemolysis, or by AB sensitization.

Snyder believed that some of the instances of feeble-mindedness in institutions may be the result of such Rh sensitivity on the part of the mother, causing brain damage to the infant. On the other hand, others believe that most children who recover from erythroblastosis fetalis will be normal.

A and B antibodies acting on the red cells of infants belonging to a blood group incompatible with that of the mother occasionally bring about a breakdown of their red cells. Because these agglutinins are large and so rarely get into the fetal circulation in great numbers, and because the agglutinogens A and B in the red cells of the infants are incompletely developed, the resulting hemolysis is usually mild. Some cases of physiologic icterus may belong in this category.

Treatment of these allied diseases, which may be grouped under the heading of congenital hemolytic disease, is by transfusion. This is merely replacement of destroyed blood. The accepted amount is 10 cc. of Rh-negative blood per pound of bodyweight when the hemoglobin falls below 80 per cent. Larger transfusions may be necessary when the hemoglobin has dropped far below 80 per cent before treatment is instituted. Care must be taken not to overload the infant, however. Transfusions are not indicated until the hemoglobin falls to 80 per cent. Dehydration should be avoided as it may play a role in the development of icterus grans neonatorum.

C. A.

1946 PROGRESS IN METHODS OF TREATMENT

ALTHOUGH no one development in medical research in 1946 can be singled out for special recognition or dramatic acclaim, a considerable amount of developmental work was conducted on problems on which fundamental research had been in progress for a long period

of time. Much of this developmental work has culminated in methods of treatment and therapeutic products which have shown experimental or clinical evidence of practical application.

A survey of the medical research reveals a lengthy list of noteworthy advances and we have tried here to review the progress made during 1946 and to indicate the trends for the future.

Details of the structure and synthesis of *folic acid,* the latest member of the vitamin B-complex to be identified as a pure substance, were released in May. In addition to macrocytic anemia with which folic acid deficiency is most commonly associated, other clinical conditions characteristic of chronic deficiencies are leucopenia, hypoplasia of the bone marrow, infections of the intestinal tract, and injury to the mucous membranes.

Streptomycin became available for general civilian use for the first time in 1946 with the greatly increased commercial production. A broad, coordinated investigative project was instituted to study benefits of streptomycin in the treatment of tuberculosis. The value of streptomycin in the treatment of tularemia and certain infections of the urinary tract has also been established by extensive clinical investigations.

Dihydrostreptomycin, derived from streptomycin, was more recently found to have as great activity against germs as streptomycin and to be even more stable.

In November of 1946, announcement was made of the isolation in crystalline penicillin of the active synthetic product and proof of its identity with natural G-penicillin (now called benzylpenicillin). The isolation of *benzylpenicillin* as the triethylammonium salt from the reaction of *d*-penicillamine (*d*-β, β-dimethyl cysteine) and the azlactone (2-benzyl - 4 - methoxymethylene - 5 (4) - oxazolone) proved conclusively that penicillin can be synthesized. The synthesis cannot yet be used as proof of the structure of penicillin as the reaction mechanism is still obscure. Crystalline penicillin having a potency of about 1,500 units per milligram became available in commercial quantities. During the year, a new preparation of penicillin with a vasoconstrictor was released for the treatment of acute and chronic sinusitis.

Erythrin, a new penicillin-like drug, which is extracted from the red blood cells of rabbits and other animals, is reported to show promise in the treatment of diphtheria and other infectious diseases.

Interest in *tropical diseases* stimulated by the war has resulted in the development of new and improved drugs for their treatment. Superior results have been obtained with Chloroquine (SN 7618) as a suppressive agent and this material has been made available under the name Aralen. Paludrine, introduced by the British, is being subjected to extensive investigation by American workers. More recently, attention has been directed to Pentaquine, an 8-aminoquinoline (SN 3276) which has shown promise as a curative agent in treating relapsing malaria. Clinical investigations are not yet sufficiently comprehensive to establish its superiority over Plasmochin.

Experimental and clinical studies are being conducted on *p*-carbamiodophenylarsenous oxide, the trivalent analog of carbasone, which has shown greater activity as an amebicide than the pentavalent compound. Sodium *p*-melaminylphenylstibonate is reported active against African sleeping sickness; the compound is being tested clinically along with melarsen oxide.

Successful results have been reported in treating certain types of epilepsy with a new drug, *mesantoin. Tridione,* another new product, has continued to show favorable results in treating petit mal epilepsy.

Many allergy sufferers welcomed several new drugs which inhibit the action of histamine, which is released by the tissues in allergic reactions. Experimentation has proved the efficacy of two recent *anti-histaminic agents,* benadryl (β-dimethylaminoethyl benzhydryl ether hydrochloride) and pyribenzamine (*N'*-pyridyl-*N'*-benzyl-*N*-dimethylethylene diamine) hydrochloride. Patients with hives, skin allergy and serum sickness type of reactions caused by penicillin and sulfonamide drugs have gained

relief with these drugs. The isopropyl analog of epinephrine has been found to be an effective orally active bronchodilator and in clinical tests has shown promise in the treatment of asthma. In France, *Neo-Antergan* (*N-p*-methoxybenzyl-*N*-dimethylaminoethyl-α-aminopyridine hydrochloride) has been developed, and is undergoing clinical tests in this country.

Therapeutic applications have been developed for a number of compounds prepared and studied by the Chemical Warfare Service. Sulfur and nitrogen mustards, known as *contact vesicants,* were found to exert cytotoxic actions on various tissues. Experiments on transplanted lymphosarcoma in mice showed that dissolution of tumors could be rapidly effected when near-toxic doses were administered, but the growth invariably returned.

The program of the Chemical Warfare Service also developed di-isopropyl fluorophosphate (DFP) which has been used successfully in treating glaucoma and myasthenia gravis.

Radioactive isotopes for biological and physical tracer studies and for experimental therapeutic use were made available from the Oak Ridge uranium pile. This constructive application of atomic energy is beginning to be widely utilized and offers striking possibilities in the exploration and solution of the complex functioning of organic mechanisms and disease. Radioactive iodine has been successful in treating thyroid cancers and certain types of skin cancer have responded favorably to treatment with radioactive phosphorus.

N-propyl thiouracil has been found to be much more effective than thiouracil in the control of hyperthyroidism. Radioactive iodine is also valuable for this purpose as it is reported to remain concentrated chiefly in the thyroid gland, its beta-rays furnishing internal radiation similar to Roentgen radiation.

Clinical observations have indicated that *rutin,* a glucoside isolated from the green buckwheat plant, is effective in treating fragile and weakened capillaries and may be of use in treating high blood pressure associated with increased capillary fragility.

Successful results were obtained in the immunization of monkeys with the first *mumps vaccine.* The vaccine is now reported to be in the final stages of development.

Experimental studies on animals have shown that *nutrition* can be a dominant factor in the incidence of spontaneous or induced tumors. Observations in dietary relationships have indicated that a low intake of choline of the vitamin B-complex could induce a high incidence of tumors in albino rats. It has also been found that a lack of milk in the daily diet of rats may influence the development of cancer of the liver.

BAL (2,3-dithiopropanol) developed by British scientists as an antidote to arsenical blister gases, is now available for civilian medical use in the treatment of arsenical poisoning. BAL (the term is a contraction for British Anti-Lewisite) acts in treating toxic encephalopathy, arsenical dermatitis and acute hyperpyrexia occurring as complications of arsenotherapy and in other types of heavy metal poisoning.

Reports on the development of *new drugs in Germany* were released during 1946 and investigations on them are being made in this country. Indications are that Amidone (1,1-diphenyl-1-dimethylaminoisopropyl-butanone-2), synthesized in Germany, is as active an analgetic as morphine. Several new drugs have been developed to relieve spasm of smooth muscle. In addition to Amethone which has been introduced commercially, β-diethylaminoethyl phenyl-α-thienylacetate hydrochloride, 1,1-diphenyl-3-piperidinopropane and others have shown promise in clinical tests in controlling spasms of the gastrointestinal tract.

Preliminary reports released from Russia on a new serum *KR,* secured from the blood of guinea pigs infected with the parasite of Chagas' disease, state that it may be effective in stopping growth of cancer cells and yet not harm normal cells.

S. C.

This Month in Medicine

PSYCHOSOMATIC MEDICINE

Psychosomatic medicine is rapidly becoming established as a profoundly important field of endeavor. Although scarcely attractive to the highly specialized physician, it has gained the attention of many students whose experiences have been on the border-line between psychiatry, neurology, psychology, and clinical medicine. One of the more interesting tools of research in this rather diffuse field has been the Minnesota Multiphasic Personality Inventory. With this analytic system, Seltzer has been able to correlate dominant personality traits with certain physical disproportions existing in "normal" college students who had been selected for their apparent normality. The physical disproportions were of such seeming insignificance as to be recognized only by careful measurement. Nevertheless, they were sufficiently influential: excesses of these physical disproportions were associated with personalities that were less stable and integrated, more sensitive and complex, and but poorly adaptable. The students having a deficiency in body disproportions, however, were possessed of personality traits making for stability, adaptability, and good integration. We have, therefore, evidence of significant relationship between physique and personality in "normal" persons.

Recently Houk and Robertson have applied the Minnesota Multiphasic Personality Inventory to the diagnosis of hypoglycemia-neurosis; that is, the personality inventory was correlated with the glucose tolerance curve. The authors observed that patients with hypoglycemia and neurosis followed a definite pattern in their deviate answers to the questions in the personality inventory. Of thirteen neurotics with hypoglycemia, twelve scored fourteen or more deviate answers to twenty selected questions. Another nine neurotics were found to have scores of thirteen or more. When glucose-tolerance determinations were done on these patients, all were found to have hypoglycemia. Hypoglycemia was suspected in four other normal persons whose scores were from eleven to fourteen; glucose-tolerance determinations confirmed this suspicion.

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MASS CHEMOPROPHYLAXIS

Mass chemoprophylaxis has been attempted by many investigators, particularly in the armed forces, and there can be little doubt that it will serve to reduce measurably the virulence of epidemics. Recently Grand and his associates presented the statistical results of their studies of the use of sulfadiazine in the prevention of rheumatic fever among navy personnel.

The investigation embraced more than 25,177 recruits, to whom a daily dose of 0.5 to 1.0 gm. of sulfadiazine was given either on alternate weeks or throughout the test period. Another group of 17,927 men were unprotected and served as controls. Although the prophylaxis did not eliminate rheumatic fever among the men, it did diminish the number of cases. The protected troops had an incidence of 0.715 per 1,000, and the unprotected controls had an incidence of 1.45 per 1,000. Thus, the sulfadiazine was effective in reducing the incidence by one-half.

In this connection, the use of mass chemoprophylaxis in the prevention of various streptococcal infections has revealed that during the course of such a campaign some strains of the infecting organisms frequently develop sulfadiazine resistance. The question arises, therefore, as to whether streptococci become resistant to sulfonamides during the course of treatment. Hartman has approached this problem in a study of forty scarlet fever patients. Nasopharyngeal cultures were obtained when the patients were admitted to the hospital and while in the acute stage of the disease. A course of sulfadiazine therapy was then administered, either to prevent the development of a

carrier state or to subdue purulent complications. Another culture was taken during the convalescent period after the sulfadiazine treatment. Cultures so obtained were tested by standard methods for sensitivity to sulfadiazine. None of the hemolytic streptococci, which were isolated following the course of sulfadiazine therapy, showed any evidence of having developed resistance to sulfadiazine. Apparently, therefore, the resistance that was observed among the troops during mass chemoprophylaxis was engendered by the use of small quantities of the sulfonamide over an extended period. When the drug is used for a brief period in large doses, as in Hartman's investigation, resistance probably is not encountered.

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PREGNANCY TESTS

A rapid chemical test for the diagnosis of pregnancy would be of tremendous clinical value. For a time the Guterman test, which was based on the color reaction of pregnandiol in urine, seemed to show promise. Recent reports, however, indicate that the test is not sufficiently reliable to warrant its widespread application.

Morrow and Benua found that a large percentage of normal nonpregnant women gave positive reactions during the luteal phase of the menstrual cycle. Furthermore, the test gave a negative finding in a normal patient seven weeks pregnant. They pointed out that when large amounts of seventeen-ketosteroids are in the urine, as in arrhenoblastoma, the test may be positive. Finally, if amenorrhoea exists without pregnancy and if the corpus luteum is functioning, a positive test may result. These findings have been corroborated in part by Reinhart and Barnes, who found that both positive and negative reports are subject to a 25 per cent error. They believe that the source of error lies primarily in individual variations in the metabolism of progesterone in both pregnant and nonpregnant women.

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TANTALUM CRANIOPROSTHESIS

The discovery of the value of tantalum as a superior closure material for skull defects was a significant advance in surgery and brought to an end a search that had gone on for more than three hundred years. It is indeed a remarkable metal, biologically inert, malleable and ductile, yet stout enough so that a sheet 0.0125-inch thick protects the brain. It may be readily cut or worked at the operating table. Indeed, tantalum satisfied remarkably the exigencies of combat surgery, wherein the outstanding virtue of any technique or device (or man) is its adaptability to unpredictable circumstances.

During the war MacKay and Russell developed a "simple, easy, and quick method of repairing cranial defects from a basic, 'ready-made,' tantalum cranioprosthesis." Although the details of the operation itself cannot be treated here, mention may be made of the basis for their method. These investigators observed that most of the calvarium consists of a composite of segments of four spheroidal surfaces, centered around the four major prominences of the skull. The radii of these major surfaces all equal approximately 2¼ inches. These curved surfaces also constitute the only real problem of cranioprosthetics, as the intervening planispheric surfaces are easily duplicated. This being the case, the authors fabricate, by hammering, a tantalum hemisphere with a fixed radius, which serves as an exemplar from which one or several cranioprostheses of various specifications can be cut. This hemisphere is sterilized with the instruments at the beginning of the operation. In practice, the surgeon simply replaces one spheroidal surface of the skull with another identical one made of tantalum. Since these spheroids always have approximately the same curvature, the basic

exemplar of equal radius eliminates the necessity of molds, casts, or intermediate preparatory craniotomies. While MacKay and Russell do not believe their innovation to be the last word, they do report success with the method in the repair of twenty-five cranial defects. Interestingly, they observe that the South Sea Islanders hit upon a similar principle ages ago when they repaired cranial defects with coconut shell.

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STREPTOMYCIN AND TUBERCULOSIS

The veteran streptomycin investigators at the Mayo Clinic recently have reported their results with this antibiotic in the treatment of tuberculosis. One report is concerned with thirty patients with pulmonary tuberculosis to whom streptomycin was administered for two to six months. In general, the patients selected for investigation had tuberculosis that either was progressive or did not respond to bed rest. Streptomycin was administered, 1.0 to 4.0 gm. per day, in divided doses given intramuscularly or by deep subcutaneous injection every three to six hours. The evaluation of results was based upon changes noted in serial roentgenograms. Of twenty patients with far-advanced tuberculosis, nine showed marked and unexpected improvement, two showed moderate improvement, and five showed slight improvement. In four, no change was noted. Twenty-six of the total of thirty patients revealed some degree of improvement. In none did the condition become worse during the course of therapy. Exudative lesions showed the most rapid improvement. The changes evidenced roentgenologically were so prompt and consistent that there could be no reasonable doubt that the drug exerts a *suppressive* effect upon the disease.

Apparently favorable responses were obtained in a variety of extrapulmonary cases of tuberculosis. Here again, the drug appears to have suppressive value. All in all, the investigators view favorably the possibilities of streptomycin in the treatment of tuberculosis; but with laudable reservation they insist that the drug should not be used as a substitute for accepted and proved therapeutic procedures.

SUGGESTED READING

Hinshaw, H. C., et al.: Streptomycin in treatment of clinical tuberculosis. Am. Rev. of Tuberculosis, **54**:191, September, 1946.

Pfuetze, K. H., et al.: Clinical use of streptomycin in the treatment of tuberculosis. Diseases of the Chest, **12**:515, November-December, 1946.

UROLOGICAL CONDITIONS OF GILBERT ISLAND NATIVES

A physician in the Navy Medical Corps reports on urological conditions among the natives of the Gilbert Islands. Venereal disease is almost unknown among these islanders; such few cases as are found were caused by transient whites. Circumcision is commonly practiced and usually consists of a dorsal slit. Hydrocele is often seen. Sometimes it is of filarial origin, but more often is caused by scrotal trauma brought about by the heroic manner in which the natives climb coconut trees. Prostatic hypertrophy was observed in only one patient, a French priest!

SUGGESTED READING

Twinem, F. P.: Wartime urology in the Navy. J. Urology, **56**:757, December, 1946.

TOXIC REACTIONS TO DDT

Reports of toxic reactions to DDT continue to appear in the literature. Hill and Damiani report the case of a patient whose death apparently was caused by exposure to the fumes of a 6 per cent solution of DDT in kerosene with which the room in which the patient worked had been sprayed. The case is of particular interest because the authors state that the clinical, laboratory, and roentgenographic findings all were similar to those of periarteritis nodosa. Since other investigators have claimed that periarteritis nodosa is a hypersensitive state induced by such sensitizing drugs as the iodides and the sulfonamides, Hill and Damiani believe that DDT likewise should be included among the drugs producing effects that simulate this condition. The assumption is therefore made that DDT possesses allergenic properties that must be considered.

SUGGESTED READING

Hill, W. R., and Damiani, C. R.: Death following exposure to DDT. N. Eng. J. Med. 235-897, December 16, 1946.

R. W. C.

Consultation Service

We offer this special consultation information service as a regular monthly feature of *Postgraduate Medicine*. Readers are invited to call on this Service for answers to difficult medical problems from members of our editorial board best qualified to help. Each question will be answered by mail and answers of general interest will be published each month.

DUODENAL ULCERS

QUESTION: Is protein hydrolysate useful in the treatment of selected cases of duodenal ulcer? Why does a common cold aggravate the symptoms of duodenal ulcer?

M. D.—Indiana

ANSWER: Casein hydrolysate or amino acid mixtures have been used in treatment of peptic ulcer with the assumption that general and local cell nutrition would be improved and consequently healing promoted. The indications for use of concentrated protein material would appear to be malnutrition or protein deficiency or when circumstances prevent giving adequate amounts of protein as food.

Systemic phenomena associated with an acute febrile infectious disease may activate a quiescent inflammatory condition of any organ. That is, changes in circulation, in body fluids, and in metabolism provoked by fever affect damaged tissue when normal cells are resistant. Transient bacteremia may be accessory to the other effects. The alterations at the site of a latent or healed peptic ulcer responsible for macerbation or renewal of activity comprise hyperemia, probable congestion and edema, elimination of protective mucus, and possible inoculation by bacteria in the blood.

INFECTIOUS FEVERS

QUESTION: When do the infectious fevers become infectious? For instance, is a child who is developing mumps liable to infect other children during the whole twenty-one days of the incubation period?

M. D.—Kansas

ANSWER: Infectious fevers become contagious under different circumstances. In the case of mumps, the contagion begins at the time of swelling and continues until the swelling has disappeared. For those diseases that have a prodromal period, such as measles, the contagion begins with the onset of the prodomal symptoms, such as sneezing and coughing, and lasts until these symptoms have disappeared. The incubation period which is the time from exposure to the onset of the clinical symptoms is non-contagious.

OSTEO-ARTHRITIS OF LEFT HIP

QUESTION: A male aged 70 has advanced osteo-arthritis of the left hip, which is painful and more or less fixed in partial flexion with marked adduction. Would subtrochanteric osteotomy, if successful mechanically, relieve or remove the pain, which is at present almost constant?

M. D.—Missouri

ANSWER: If the physical condition of the patient is such that he can stand major surgery, the procedure of choice would probably be an arthrodesis of the hip of intra- and extra-articular type. The use of a long Smith-Peterson nail across the joint would probably decrease the necessary immobility. Subtrochanteric osteotomy and cup arthroplasty would be the next procedures to consider. The results with arthrodesis are usually the

most consistently good. If the patient is not considered a good surgical risk, one might try traction with Buck's extension and rest in bed for a few weeks followed by the use of crutches or a cane. Although this may give temporary relief, the chances of recurrence of pain and flexion deformity are great.

PENICILLIN REACTIONS

QUESTION: I recently had a patient to whom I gave penicillin throat lozenges (1 two-hourly for six days) for a streptococcal tonsillitis. The tonsillitis settled down at the end of a week but the patient's tongue became swollen and painful as if the superficial layer had peeled off. This healed in one week. The patient was not anemic. I concluded that the tongue condition was due to the penicillin. Would you kindly advise me on this?

M. D.—Michigan

ANSWER: In answer, let me state that throat lozenges and troches are all made up with calcium penicillin and that the hydrogen-ion concentration of calcium penicillin is a little on the acid side. This, therefore, should not cause the reaction described by the questioner. Rather, I believe that it is a localized allergic reaction of the tongue tissues to the penicillin. Similarly, use of penicillin in the eye will occasionally give rise to a contact dermatitis of the conjunctiva and lids.

PERNICIOUS ANEMIA

QUESTION: A man of 51 has had pernicious anemia for fifteen years, and for three years has received doses of liver extract. The symptoms of subacute combined degeneration have improved under treatment. His blood count is now five millions and his color index 1.16. Is it wise to continue with 4 ml. of liver extract weekly?

M. D.—Oklahoma

ANSWER: The proper maintenance dosage of an effective fraction of parenteral liver extract is that amount which prevents macrocytosis of the erythrocytes and also the advance of neurologic symptoms. In general 15 units of liver extract injected intramuscularly at intervals of one to two weeks will accomplish this result.

EFFECTS OF STILBESTEROL

QUESTION: A woman of 51 had an erythematous condition of her face. A specialist prescribed 1 mg. stilbesterol daily for two months, then one month's rest. She now has uterine bleeding, though her menopause was three years ago, and she is worried about the possibility of pregnancy. Can I reassure her that stilbesterol does not cause ovulation after the menopause and that pregnancy cannot supervene?

M. D.—Illinois

ANSWER: Stilbesterol will not cause ovulation in a woman three years beyond menopause. This period of three years is taken to mean complete amenorrhea until the bleeding which was induced by stilbesterol through the formation of a hyperplastic endometrium. The likelihood of pregnancy in a woman three years beyond the onset of menopause will not be enhanced by giving stilbesterol.

ANGINA PECTORIS

QUESTION: What is the pathological condition in angina pectoris? What is the clinical distinction between angina pectoris and coronary thrombosis?

M. D.—Pennsylvania

ANSWER: Angina pectoris, usually referred to as a clinical entity, is a manifestation of coronary arteriosclerosis. It is due to the anoxemia of the heart muscle resulting from the insufficient coronary circulation because of the arteriosclerosis. Coronary thrombosis denotes a complete occlusion of a coronary artery, with the formation of a clot in the vessel and usually followed by infarction of the heart muscle. Angina pectoris occurs in this condition also, but the pain is more severe and of longer duration—usually more than one-half to one hour—than in coronary arteriosclerosis without occlusion.

Men of Medicine

Missionary To The Heathen

DR. ANTON J. "AJAX" CARLSON started out as a boy to be a missionary to the heathens. And he is still at it. At the age of 72 his definition of the word "heathen" has changed, but his spirit has not.

From his laboratory and office on the third floor of the Abbott Hall on the University of Chicago campus, where he is still carrying on research as Professor Emeritus of Physiology, he sallies forth on frequent missions to attack human ignorance and stupidity.

The songs and sermons of the old Swedish Lutheran Church whetted his zeal and ardor when, as a lonesome boy of seven, on the North Sea Coast, he herded sheep and watched the ships sail by for unknown ports.

He was born on a farm near Svarteborg—not far from Goteborg. His father died when he was five years old, leaving his mother with seven children and no money to support them. Anton, third from the youngest child, hired out to a neighboring farmer. But sheep-herding was no life for a vigorous youngster, and he says "the everlasting baa, baa, baa of the sheep" drove him wild. Deeply embedded was a strong desire for an education but, because of his circumstances, he know it was impossible in Sweden.

The passing ships filled him with ideas. If he could get away to America, perhaps he could rid himself of this gnawing desire. He stuck it out until he was 17. His brother had gone to America, and Anton followed, to Chicago to take up carpentering. But his urge for an education remained strong, so after a year and a half at his trade, he entered Augustana College in Rock Island, Ill.

At Augustana he luxuriated in the religious zeal of the church and the community. He steeped himself in Latin, Greek, religious lore, and philosophy. But religion and philosophy did not rest too well on his mind and, when a professor of geology invited him to take part in studying a research problem—how the wind altered the contour of the earth—there was a reconversion.

Anton J. Carlson*

"For the first time I realized that all information is not just in books, that information in books is not always reliable," he says. "All that stuff—Latin, Greek, history, philosophy, religion—is just damn blah, blah, blah."

Carlson stayed at Augustana to receive his bachelor and master of science degrees, and then left for Stanford University to receive his doctorate of philosophy in biology. After his graduation with the doctorate he did research in biology for the Carnegie Institution in California, and then was sent to Woods Hole, the biologist's paradise.

Among biologists at that time there was a sharp

*Professor Emeritus of Physiology, University of Chicago; well known for his research on human physiology and particularly the reactions of the stomach; author of "Control of Hunger in Health and Disease"; 94th president of the American Association for the Advancement of Science.

controversy as to the origin of the heart beat. Did it start in the heart muscle or the nerves? The argument was something like the medieval controversy as to how many angels could stand on the point of the pin.

"Let's get the evidence," he said. He worked with the horseshoe crab as an experimental animal, and arrived at a verdict.

"It begins in the nerves," he said, "of the horseshoe crab."

Commenting on this guarded statement, he says, "Scientists must always look for the evidence, and examine the evidence critically to see if it is sound."

While he was enroute to Woods Hole, he met the late Professor G. N. Stewart, former head of the Department of Physiology at Chicago.

"I was in a saloon on Cottage Grove Avenue in Chicago (commonly frequented by University of Chicago faculty men) with some of my colleagues," Dr. Stewart related. "A brawny Swede breezed in.

"One of my associates hailed him with 'Hello, A. J.! Have you ever met Stewart?' 'No,' answered Carlson as we were introduced. I invited him to join us in some beer. He did, and I was greatly impressed with his capacity—both for beer and physiology."

Also impressed by his scientific method of attack in his Woods Hole research, Dr. Stewart invited him to join the Chicago faculty. He was appointed associate in physiology in 1904, assistant professor a year later, associate professor in 1909, and professor of physiology in 1914, when Dr. Stewart left for Western Reserve University.

In making his teaching dramatic and effective, Ajax would often pull out every stop. He could turn on and off his Swedish brogue at will—as he still does whenever he wants to create an effect.

He always lectured to college freshmen in physiology because he believed the "babes" should get the best start, and who could do any better than the head of the department himself?

When a student would offer as a fact something that created some doubt in his mind, Ajax would gaze at him, glasses propped on his forehead, and arms waving, would shout, "Vot iss de effidence?"

This caustic "Vot iss de effidence?" has made many a scientist cringe. Dr. Carlson has appeared in the audience of innumerable scientific gatherings, and it is said he has never fallen asleep at one of them. Although he has often been bored, he did not want any scientist to put anything over on him.

At one time Serge Voronoff was reporting on rejuvenation of humans through the grafting of monkey glands. Ajax sprang to his feet and shouted: "I knew of a case of a rejuvenated man in the United States who felt young until he received his doctor bill. Dot vos so high he suddenly felt old again."

Not only was Dr. Carlson critical of his students' method of thinking, but he was fiercely intolerant of laziness, tardiness, or any other sign of inattention or lack of interest. In the flapper days when a young woman student powdered her nose in the classroom, she was immediately told to get out. Tardy students would find the classroom doors locked. At one time, to pep up his students, he tried to hold classes at 6 o'clock in the morning, but that effort failed.

He was as fond of pranks as he was fond of being severe. One time he announced to a class that he was going to test their accuracy of observation. He placed on a table a glass of nauseous, vile-smelling liquid. He dipped in a finger, and put his finger in his mouth, without any change of facial expression.

"Now each of you will do exactly as I did," he directed. They all obeyed, and their faces contorted in violent distress.

They wondered how that damn Swede could take it.

"But," said Ajax, "you failed to observe that the finger I dipped in this solution was not the one I put in my mouth. Next time please observe more carefully."

He was as tough with his colleagues as he was with his students, and a temperamental, hard-driving worker.

Just back from Europe after World War I, where he had served with the Army, and subsequently the American Relief Administration, Dr. Carlson decided to do a series of investigations of the visceral sensory nervous system of lower animals. He recruited one of the younger men of the physiological faculty as his assistant.

After eating a hasty breakfast, they would get to work at 8 o'clock. They then would work without eating and without stopping until 3 o'clock the

next morning, snatch a bite of ham and eggs, sleep, and renew the ordeal the next day. This went on for weeks and months—Sundays and holidays included.

Neither Carlson nor his assistant would see their families for weeks on end. Carlson would not even carry on a conversation unless the subject applied to the work at hand.

From this experimental work Dr. Carlson and his assistant produced such a volume of reports that the editor of the journal to which they were submitted could not believe the two had actually done the work.

Shortly afterward the assistant in this research was given an assignment by the Rockefeller Foundation in Germany. There was still a volume of work to be done, but the temperamental Carlson's interest lagged. When anyone wanted to find him, he would be at the Quadrangle Club (Faculty Club) playing bridge during the day and most every night until 11 or 12 o'clock.

Dr. Carlson has been as outspoken with the administration of the University of Chicago as he has with his students, colleagues, and other fellow scientists. As a member of the American Association of University Professors, he has had many a set-to with the officers of the university. Taking part in a debate on the subject of freedom of teaching, he said, "So far as I am concerned, I don't look up to deans, nor do I look down on them. I just look at them."

When President Hutchins was new at the University, he proposed to eliminate all tenure privileges of the professors.

"I was at the meeting," Dr. Carlson relates. "President Hutchins argued that such a step would keep professors on their toes.

" 'President Hutchins,' I said, 'aren't you slightly confused in your anatomy? What you mean is that it will not keep them on their toes. It will keep them on their knees'."

President Hutchins' proposal didn't go through.

"But I get along with President Hutchins fairly well," Dr. Carlson says. "He doesn't understand science or the method of science. His face is toward the past. He is looking for the answers of the problems today in his 100 great books—but they are not there.

"The answers are in a better understanding of man instead of in emotions and traditions of the past."

Dr. Carlson says that America is scientifically illiterate. The method of science in education is neglected. People do not know how to scrutinize, analyze and improve the facts.

"Science in the schools and colleges is a quiz kid program," he says, "and in all mankind, the conditioned reflex toward the past is an iron chain that binds us."

In failing to apply the scientific method, Dr. Carlson says, educators drown children with facts, destroying their power to think.

"Young children have a wise stage—the age when they are everlastingly asking why that is so, and why this is so, and how this or that thing happens," Dr. Carlson says, "and we drown them with facts. The result is that we educate out of them their fund of mental curiosity with which they are born."

To get at the facts of human physiology, Dr. Carlson frequently uses himself as a guinea pig. He would starve himself for as long as five days to determine the reaction of his stomach in unusual situations. One day near the end of one of these periods of self-starvation, he had a cannula in his mouth, the end of which was held against the parotid duct to measure the amount of saliva flow. He had ordered a steak with mashed potatoes, gravy, and all the trimmings. Just as his assistant walked in with the feast and it caught Dr. Carlson's eye, the saliva squirted out through the cannula in a heavy stream.

Many times while doing his famous experiments on the motility of the stomach, he could be found in the laboratory with a tube with a condom on the end, down his esophagus, and inside his stomach recording the movements of that organ.

In those experiments he had a streak of luck, rare in the life of any scientist.

One of his colleagues discovered a barber by the name of Fred Vleck, who in childhood had swallowed lye, which had closed his esophagus. To save his life, a surgeon had opened a window to his stomach so that Vleck chewed his food, and after he had obtained full satisfaction, spit it out into a tube that entered the stomach through the window.

After a drawn-out controversy with the University administration and the trustees, Dr. Carlson persuaded them to employ Vleck as a human guinea pig. He looked into the action of Vleck's stomach for 13 years until the man died of cancer of the esophagus, caused by the original burn.

Carlson fed him everything imaginable to find out how the stomach would react to it, from paraffine to whiskey. But the man was so nervous that everything Carlson did to him he had to do to himself in the man's presence.

He found that when the stomach is empty it begins to contract periodically, and that the contractions are not controlled by the brain or other portion of the central nervous system, and neither by sight, smell or taste of food.

A person may or may not be aware of the contractions of his stomach. Hunger, in fact, is distinct from appetite, which arises from the stimulation of the nerve endings of the mouth. There is, in a sense, he found, two forms of hunger—brain hunger and stomach hunger. These researches into the reactions of the stomach culminated in Dr. Carlson's greatest work, "Control of Hunger in Health and Disease."

In his work he came to the conclusion that periods of starvation of perhaps a week, were definitely good. His periods of fasting were as invigorating to him "as a month's vacation in the mountains," he said.

In somewhat different sense he believed the problem of feeding a hungry world is the number one problem that humanity faces.

This was impressed on him after World War I, when, as a member of the American Relief Administration, he visited all countries from the Adriatic to the continent of Asia.

"Every civilization in the past has gone under for failure to conserve the soil, and all species of animals tend to reproduce faster than the land will supply food to suport them," he says. "Very soon the United States will need for itself all it can produce for an optimum of nutrition because of the increase in population and the waste of soil.

"We must think ahead, not 10 years, not 100 years, or 1,000 years, but 10,000, if the human species is to be saved from starvation. Ignorant Americans turn up their noses at the Chinese, Dutch, and French peasants who put human night soil back into the land while we let it slip away from us into our rivers, lakes, and the oceans."

Probably more than any other American who saw Europe after World War I, he was privileged to see the "terrible backwash of the war"—the destitution, misery, and starvation. He was in Paris during the Versailles Conference, and said he was impressed "by the insincerity of Clemenceau, Lloyd George, and Orlando, who drew up the so-called peace."

"My conclusion was that war is an excellent preparation for the next war, and not a preparation for peace," he says.

This was his explanation of why, before Pearl Harbor, he took the platform for the America First Committee. He did not think American democracy could survive another war.

He did not hold with the Nazi ideals. Far from it. He believes that the human race is one, whether "white, black, yellow, brown, or tan." But, "it will take 10,000 years to work off racial prejudices, and by that time the whole species may be dead, as a result of our own stupidity."

During World War II he worked to the full extent of his time, energy, and ability in the service of such agencies as the Office of Price Administration and the Office of Scientific Research and Development. His latest project with the OSRD, which has been taken over by the National Academy of Sciences, is to find something better than the seeing eye dog as an aid to blinded soldiers.

He has served with the Federal Trade Commission, and for 30 years with the United States Food and Drug Administration, which he believes to be the finest of federal agencies. "When I am sure of my ground in fighting humbug and dangers in medicine, I go all out," he says.

In the last four years he has actively championed the cause of the makers of oleomargarine fortified with Vitamin A, against legislation limiting its use. He says the restrictive laws "touching the production, distribution, and consumption of margarine, are still in our statute books, and still render it more difficult for many people to secure adequate nutrition."

Dr. Carlson, as president of the Research Council

on the Problems of Alcohol, deplores the refusal of many doctors to treat alcoholics. He urges "an entire change in the social attitude and public understanding of the alcoholic problem" and points out that a recent survey of the facilities for treating alcoholism in New York City showed that fewer than 40 per cent of the doctors cared to handle alcoholic cases. "Yet, no matter how contemptible or how down-and-out a person may be who has contracted pneumonia, the medical profession would treat him."

He says that "as long as society looks on alcoholism as a sin, the doctor will look upon it as a moral issue and one that is outside his field. Perhaps a complete understanding of the causes of alcoholism would render this malady no more a sin than say, tuberculosis."

Ajax drinks and can take it strong—on occasion—and often to the amazement of colleagues with less steel in their sinews. But these occasions are not frequent.

He drinks primarily to relax, especially when he is at his cabin in Michigan, where he and his wife and family, as well as his colleagues and friends, make pleasure trips in the winter and summer. Using his talents as an ex-carpenter, which are equal to that of an excellent cabinet-maker, he built the original cabin. Mrs. Carlson, however, was not satisfied with it, so she had a log cabin built nearby. Dr. Carlson constructed the stairway, which is considered a fine piece of craft work.

He is uncanny as a woodscraft man. In the dead of the night he can find his way through the woods without a light or compass.

There is a tradition that Dr. Carlson is fond of breaking the ice and bathing in the cold water of the streams near his cabin.

The legend began when he was at the cabin with a guide and two of his staff members. The two slept upstairs, and he and the guide below. The guide snored so loudly that he couldn't sleep. Toward sunrise, he became impatient, bounded out of bed, stripped off his pajamas, and yelled at the startled sleepers above: "Anyone who can't do what I do is a sissy."

With a shout he ran out the door, and slammed it behind him. The shivering, sleepy men upstairs looked out through a crack in the cabin wall and saw Ajax break the ice and wade in above his waist.

At another time his picture was taken with Dr. Andrew C. Ivy, famous Chicago physiologist and former student, standing waist-deep in icy water on a cold winter day. But he does not make a habit of too many frigid dips.

In full vigor of activity, rushing from one city to another on business, and from one speaking engagement to another, and alternating this with research problems as important as any he has ever undertaken, Dr. Carlson is a staunch defender of the worth of humans past the ordinary "retirement years."

"By keeping in idleness older workers who can still perform useful labor, we are not only wasting valuable human resources," he says, "but we are contributing to biological parasitism in, and degeneration of, human society. For man is no exception to the biological law that existence without effort, without struggle, impairs the species."

He still is interested in youth; and the possibilities of youth. He has taught young people for nearly 50 years and still spends some time in teaching.

"Certainly, I am interested in youth, for some day a teacher of freshmen will come face to face with a budding genius, perhaps even greater than Galen, Gallileo, Newton, or Pasteur," he says. "Teaching is always an exploration, an anticipation, a challenge, a joy, and never a drudgery."

He not only believes in the hope of youth; the usefulness of advanced age, but the need for greater education for adults, to clarify their thinking.

Dr. Carlson lives with Mrs. Carlson in a modest home not far from the University. He has two sons—Alvin, a surgeon in the Miami Valley Hospital in Dayton, Ohio, and Robert, in the advertising business in Chicago, and a daughter, Mrs. Alice Esther Hough. He has had numerous honors and has held important posts in many scientific, medical, and other societies. One of his more recent distinctions was that of 94th president of the American Association for the Advancement of Science.

He is living honestly and vigorously according to the full dictates of his conscience, seeking the truth, looking for the evidence, weighing and analyzing, discarding the untrue, and trying to make wishful thinkers, "softies," blind followers of tradition, and other "heathens" see the light.

Book of the Month—A Report

AN INTEGRATED PRACTICE OF MEDICINE*

A Synthesis of the Present Material of Everyday Practice

Success of clinical medicine requires appreciation of the unique character of the individual plus comprehension of his ailment and the reaction of his body to it. These prerequisites cannot be realized from application of rigid rules. Medicine is not an exact science, but rather a subtle combination of elements in which knowledge is subjected to the full play of intuition and imagination. Efficacy of a therapeutic program is determined, first, by exactness of diagnosis, and second, by the understanding skill with which the medical arts and sciences are incorporated into a regimen for the particular patient. In conditions such as scarlet fever, rheumatic fever and tuberculosis, for instance, responsibilities extend beyond termination of the acute phases of disease to projection of psychic, emotional, social, and economic consequences and preparation of the patient for necessary adjustments.

Mechanisms of the body are complex and the extent of medical knowledge vast. No man can hope for complete mastery of either in all their ramifications. As a practical matter in many situations, the best he can do is to know where to turn for the information he wants at a given time. Yet every physician who has sought guidance from books has been bogged down at some time by the lack of order in medical literature. Perhaps he has even sworn to himself that when he had the leisure he would attempt to coordinate and systematize the particular field of his special interest. Others have felt the same way.

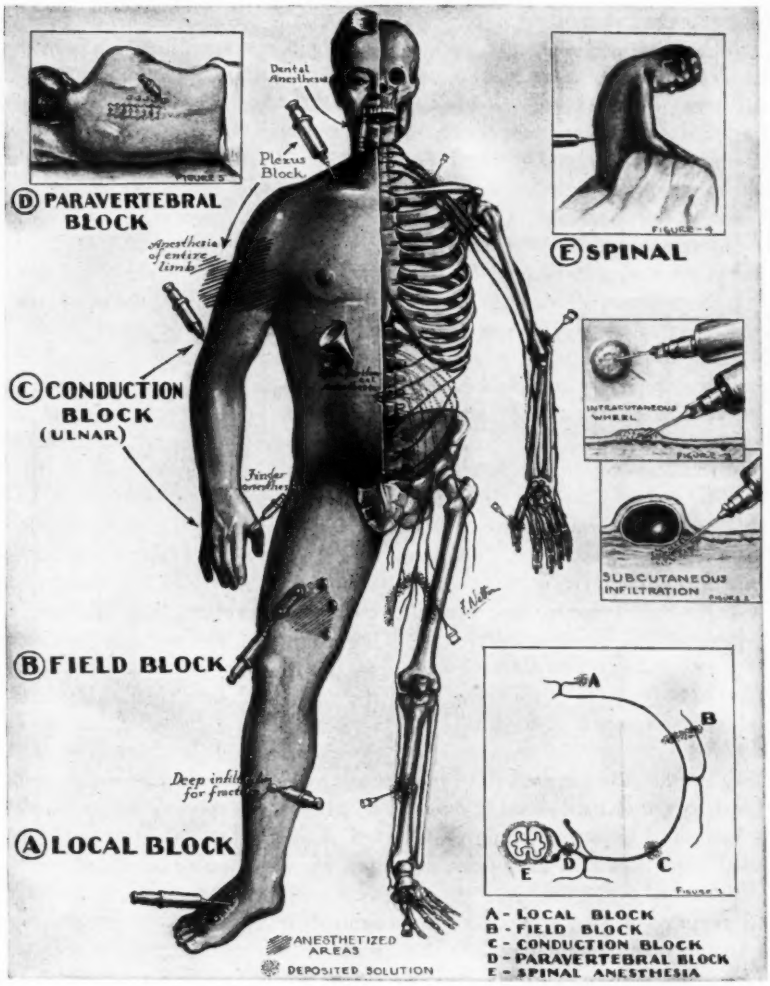
From time to time physicians have attempted to bring order out of chaos. Two notable coordinators were French and Cabot. But as recently as last year the Commonwealth Fund reported that:

> *No short-cut to the integration of specialized knowledge into comprehensive medical care has yet been devised, but until this problem is solved medicine—and therefore training for medicine—will be inadequate.*

This twofold inadequacy is emphasized by the trend towards the extremes of specialization, a trend that is accelerated by both the complexity and the volume of medical knowledge. If a man cannot master the whole, perhaps he can assimilate a part. That is the great advantage of specialization. The dangers are impairment of the doctor-patient relationship and actual deterioration in medical care. The patient may no longer entrust the matter of his health to a single practitioner, but in effect, become his own diagnostician, choose the specialist to treat the ailment which the patient decides he has. On the other hand, there may be a tendency for the patient to lose his identity as an individual in the eyes of the physician and be looked upon as a case of this or that.

In the teaching and publishing fields, at least, are indications that the trend towards overspecialization has reached its peak. During the next decade, young doctors specializing in various branches of medicine may be forced into more general types of practice by the increasing demand for the family physician. Dr. Harold T. Hyman and the W. B.

*An Integrated Practice of Medicine. A complete general practice of medicine from differential diagnosis by presenting symptoms to specific management of the patient. By Harold Thomas Hyman, M.D. Four volumes and Index. 1,184 illustrations. 4,336 pages. W. B. Saunders Co., Philadelphia. 1947. $50.00.



Illustrations from Hyman: An Integrated Practice of Medicine

Nerve block, a study of basic methods. Showing on the two sites of the body the surface appearance and anesthesized areas and the course of the nerves and actual site of deposit of the anesthetic solution.

Saunders Company must have had these men particularly in mind when they laid out the broad outline of *An Integrated Practice of Medicine*. The appeal of the four-volume set is to general practitioners to whom it is dedicated, and to the specialists desiring a ready reference to other fields.

Dr. Hyman is an internist in New York City, and an associate Professor of Pharmacology at Columbia University College of Physicians and Surgeons. He has gathered about him a group of well-qualified New York practitioners and specialists to collaborate in this ambitious program of integration of medical knowledge. The volumes are made up of 25 sections, each devoted to a clinical specialty. In general each section was written by a general practitioner, a specialist, and Dr. Hyman. The authors have not attempted a catalogue of recommended remedial agencies or

technics, but have expressed personal opinions concerning the usefulness or uselessness of various methods of therapy. On controversial matters universal agreement is not expected and Dr. Hyman invites correspondence from readers who maintain opinions opposite to those expressed in the book.

The sections of the book are grouped somewhat heterodoxically under five headings: (1) Bodily injuries and bodily responses to injury, (2) Disturbances of the systems of communication and coordination, (3) Disturbances of end organ systems, (4) The technics of medical diagnosis and therapy, and (5) Prognosis.

The first heading comprises six sections: (1) General reactions of bodily tissues, (2) Infection, (3) Allergy, (4) Neoplasms, (5) Disturbances of metabolism, and (6) Poisoning.

The second heading includes (1) The circulatory system, (2) The Blood and blood-forming organs, (3) The organs of internal secretion, (4) The Nervous system, and (5) The eye.

The third heading covers (1) Digestive system, (2) Respiratory system, (3) Urinary system, (4) Male reproductive system, (5) Female reproductive system, (6) Obstetrics, (7) Pediatrics, (8) Skeletal and locomotor systems, and (9) Tegumentary system.

Under the fourth heading are grouped (1) Physical diagnosis, (2) Laboratory methods, (3) Medical therapeutics including pharmacotherapy, and (4) Surgical therapeutics. The fifth heading is devoted entirely to the art of prognosis.

Each section is prefaced with a brief discussion of the involved anatomy and physiology. For the most part pathology is given in bare outline. In many sections, when the subject matter is inexorably linked with normal function, pathologic physiology is included in the introductory chapter. The topic of uremia, for instance, appears in the first chapter of the section on the urinary system. Discussions of various diseases proceed along fairly common lines.

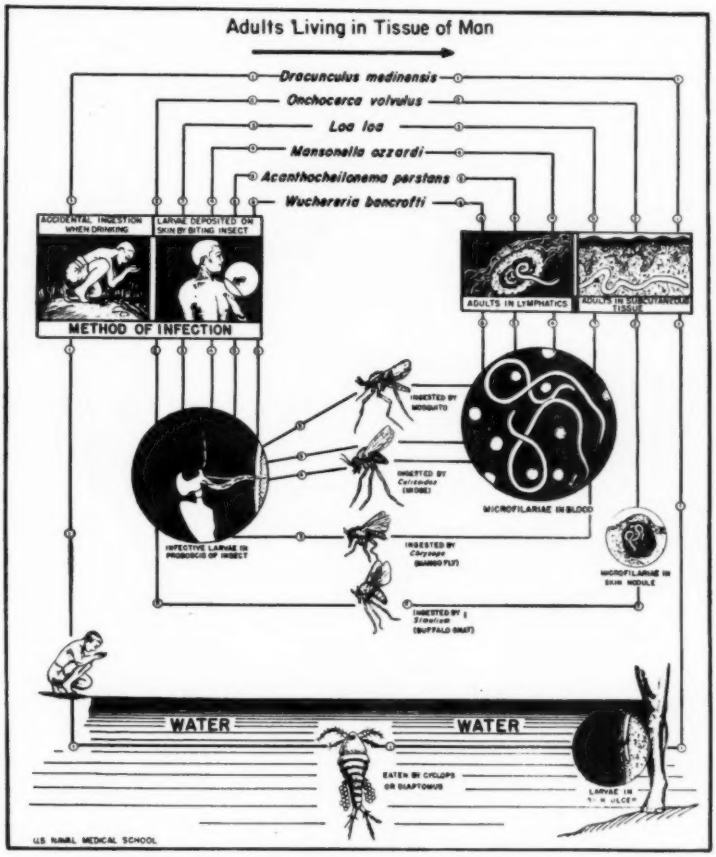
The second element in each section is a discussion of the special methods of and examination peculiar to the specialty or system under consideration. In the description of clinical manifestations of disease, emphasis is on asymptomatic stages and early symptoms and signs. In the symptomatic phases, the accent is on herald manifestations, such as Koplik spots and hyperemia of the nasopharynx and conjunctiva, which occur in measles, a day or so before cutaneous eruption. Apparatus and solutions necessary for performance of routine laboratory tests are given, together with steps in the procedure and guides in interpretation.

The closing portion of each presentation is devoted to therapeutics. Prophylactic measures, specific treatment and symptomatic therapy are all taken up for each entity. Technics of therapy are summarized or given in detail in the final volume. When specific therapy is utilized for a single purpose, details are transferred to the section devoted to that subject. Thus the material on anti-infective agents appears in the section on infection; digitalis and quinidine are dealt with in the section on circulatory diseases.

An Integrated Practice occupies an intermediate position between a single medical text and the voluminous encyclopedia. There is no exact counterpart in recent medical literature. The outstanding distinguishing feature is the differential diagnosis tables. The editor has attempted to delineate the problem to the reader as a patient would to his physician. Until the significance of a presenting symptom or sign has been interpreted there is no basis for therapy or prognosis. An immense amount of labor has gone into the production of differential diagnostic tables illustrating many symptoms and signs. These tables alone are worthy of collection and separate publication. Whenever possible individual signs and symptoms, especially symptoms presenting complaints, are isolated and the differential diagnosis is given in tabular form. In general each table is placed with the clinical condition with which the symptom or sign is most commonly associated; for example, the differential diagnosis of headache appears with Migraine.

The tables are confined to two columns, the left-hand column listing the possible causes for production of the symptom, and the right-hand column containing a telegraphic description of clinical manifestations and diagnostic features, together with suggestions for further investigations leading to a definitive recognition of the specific disorder.

After elicitation of positive findings the tables permit diagnostic possibilities to be narrowed down



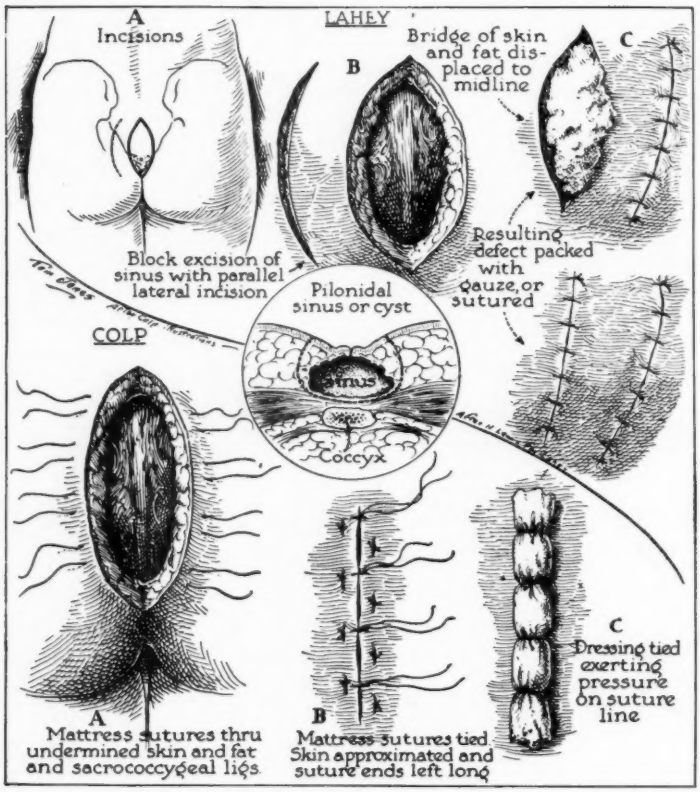
Life cycles of important human roundworms.

to a few subjects. When diagnosis has been defined page references lead to material which provides guidance toward prognosis and a therapeutic program.

Since a set of this type is intended primarily as a work of reference the accessibility of the material is important. In *An Integrated Practice* the integration is accomplished by the tables of differential diagnosis, by the cross references which appear throughout the text, and by the context which emphasizes, in each separate presentation, the broad systemic consequences of local disturbances as well as local manifestations of systemic disease.

The books are well indexed, each volume individually and all collectively. A separate desk index, really a fifth volume, is included with the set. This fifth volume, in addition to a general index, contains a special index of differential diagnosis so that any particular symptom or sign may be located rapidly. Thus the publishers have sought to facilitate finding answers in the book for whatever questions the physician may have in mind.

In his preface Dr. Hyman states his cardinal aims as (1) delineation of the broad fields of general practice, (2) arrangement of material in the chronologic sequence of everyday practice, and (3) integration of the various subjects so that each discussion focuses consideration of the human



Operative treatment of pilonidal sinus.

being as a biologic entity. The work was attempted, he says, to "correlate the clinical aspects of the practice of medicine for medical students, internes, younger practitioners of medicine, physicians who have been diverted from civilian to military practice, and for those who have spent their lives caring for home communities. It is the hope that tangible data obtained from the basic sciences may have been thoroughly fused with the broader physiologic, economic, sociologic, and humanitarian aspects of the doctor-patient relationship."

These aims are laudable, but in attempting to integrate all of medicine Dr. Hyman sometimes falls into the same pitfalls that have entrapped his predecessors, oversimplification and a condensation so rigorous that only generalities remain. That he falls short of his goal is no discredit. The integration of medicine is something scarcely to be accomplished by a book or series of books.

An Integrated Practice does, however, force attention to the fact that there are multiple causes of bodily reactions. It may suggest a line of investigation to follow in elucidation of obscure symptoms.

This is an altogether new postwar text. The material is abreast of the times although it is still too soon to expect proper evaluation of the contributions of war medicine. The work of Dr. Hyman and his collaborators represents in its own way a swing of the pendulum from specialization. It truly considers the patient as a whole.

What Other Editors Think

Editorial Evaluations of Current Contributions to Medical Progress

BLOOD PRESSURE AND AGE

It is important to interpret correctly the significance of blood pressure findings in individuals over fifty. If the physician has the opinion that the normal blood pressure in this age group is the same as in the younger group, he will label those with moderate elevation as pathological and may cause the patient needless concern.

Two points of view as to normal blood pressure in advancing age have been expressed: one, that it is the same as in youth, and the other, that it tends to increase with years. A rather general view is that a person is entitled to a systolic blood pressure of 100 plus his age. Is this correct?

An article by Russek and Zohman, in reporting the results of blood pressure readings on 3,691 men between the ages of fifty and ninety-five, confirms other reports that the systolic blood pressure does increase with age, whereas the diastolic remains about constant. Their figures show an increase in systolic pressures from 138.9, on an average, for the fifty to fifty-four age group, to 164 for the eighty-five to ninety-five group. The average diastolic readings, however, remained around 87 to 90 in all the groups over fifty years of age.

It is reasonable to explain these findings, partly at least, as due to the loss of elasticity in the aorta. It is the elasticity of the arteries, of the aorta particularly, that maintains blood pressure during diastole. Any appreciable loss of this elasticity would tend to a lowering of diastolic pressure, and a compensatory increase in systolic pressure to maintain normal physiologic circulation, would be expected.

If normal blood pressure readings are the average obtained in the examination of large groups of presumably normal individuals, then we may conclude that systolic pressures ranging from 140 in individuals fifty years of age, to 164 in those over eighty-five, can be considered normal, and, roughly, an individual is entitled to a pressure of 100 plus his age.

Minnesota Medicine, Vol. 29, P. 1253

SYPHILIS AND PENICILLIN

In the course of penicillin therapy, problems arise in connection with the penicillin-resistant case and in matters of relapse, reinfection and reactions. Public health aspects, including the question of the returning veteran and marriage, are topics of concern in connection with penicillin therapy. These and other matters must be carefully considered, especially in the light of the gradually increased dosage of penicillin that is being recommended from time to time following careful studies of treated cases. Some of these patients did not receive enough penicillin to cure their syphilis and have relapsed or will relapse.

The matter of relapse is of special significance. In the group of clinics sponsored by the National Research Council and the United States Public Health Service the cumulative percentage failure at the end of eleven months after treatment varied from 15 per cent with a dosage of 2,400,000 units of penicillin to 62 per cent with one of 600,000 units. About 10 per cent of these failures were actually due to reinfection, but the rest were relapses. Various treatment schedules were used in the different cooperating clinics and in general it can be said that there were fewer failures when both arsenic and bismuth were used in combination with the penicillin.

Another complication has been added by the changing character of commercial penicillin. Various fractions of penicillin have been found and designated G, X, F, and K. Penicillin K is relatively inefficacious, since it is rapidly destroyed in the body; this assumes significance because of the fact

that certain commercial penicillins have recently shown an increasing content of penicillin K. It is also not known as yet whether increasing purification of penicillin removes some of the substances that have great therapeutic activity.

As a result of reviewing these cases in the various cooperating clinics it has been suggested that for seronegative primary syphilis the minimum dose of the at-present-available penicillin should not be less than 3,600,000 units, given intramuscularly in doses of 40,000 to 60,000 units at two-hour or three-hour intervals. For seropositive and early secondary syphilis a dose of not less than 5,400,000 units is recommended. If a relapse occurs, arsenic and bismuth should also be given when the course of penicillin is repeated. Penicillin by mouth is not advocated. Thus, the treatment of syphilis by penicillin has repeatedly been modified as further study of treated cases has progressed.

Emphasis is placed on the fact that the present recommendations are only tentative and are subject to revision as the results of treatment are further studied. The eventual value of penicillin in syphilis is still uncertain, and its ultimate status will not be established for several years to come. To be sure that syphilis has been successfully treated by any new procedure requires a long period of observation, measured in terms of years, not months. Every physician thus has a particular responsibility for the careful follow-up, serologic and clinical, over a period of years of every penicillin-treated case of syphilis that he sees, whether the penicillin was received in civilian life or during military service.

The New England Journal of Medicine, Vol. 235, P. 952

INFECTIOUS LYMPHOCYTOSIS

In 1941 Smith in America drew attention to a benign and probably infectious lymphocytosis appearing as an acute or chronic disease in children. The acute cases had a vague and varied symptomatology, but a sharp lymphocytosis was always present. The chronic cases usually followed an infection of the upper respiratory tract; there was a low, persistent pyrexia, vague malaise and anorexia, and often spasms of peri-umbilical pain; a persistent lymphocytosis lasted a month or more; eventually the whole disturbance settled down, and there were no complications.

Duncan described an acute case in a girl of five years, beginning with acute abdominal pain and rigidity; there was no enlargement of lymphatic glands, liver, or spleen; there were 29,600 lymphocytes per c.mm., sternal puncture showed increased cellularity with 86 per cent lymphocytes, platelets were rather low, but red cells and hemoglobin were normal; the Paul-Bunnell (heterophile antibody) reaction was not significant. The acute symptoms subsided in a few days, but the pyrexia and the lymphocytosis persisted for a month. Later Duncan reported two cases in young adults, and added a morbilliform rash to the clinical picture.

Lorenz and colleagues report two more cases in children with peak counts of 47,500 and 58,000 lymphocytes per c.mm., and clinically only mild respiratory affection; sternal marrow was normal in these patients, with no lymphocytosis; the Paul-Bunnell reaction was positive up to a titer of one in eighty, but this is too low for a diagnosis of infectious mononucleosis. Steigman reports an outbreak which involved six children in one village in southern England; here cervical lymph-glands were notably enlarged and there was protracted lymphocytosis, but all recovered without incident. Smith says the disease is contagious and infectious, with an incubation period of twelve to twenty-one days.

There are already several known causes of lymphocytosis in children. Kato pointed out that from three months to four years of age lymphocytes are normally more numerous than polymorphs. A well-marked lymphocytosis has been recorded in whooping-cough, rubella, and mumps after the initial stage. Infectious mononucleosis is common in children, and it is likely that several cases of infectious lymphocytosis have been classified with this disease—for example, Thelander and Shaw's cases of infectious mononucleosis with signs of meningeal irritation, which had a lymphocytosis and negative Paul-Bunnell tests.

Here, then, is a benign almost certainly infectious condition, mainly affecting children, with a very variable clinical picture, sometimes simulating acute abdominal or nervous disease at onset; and sometimes only a mild respiratory tract affection;

pyrexia may be protracted and the blood shows a pronounced lymphocytosis. The Paul-Bunnell reaction is not significant. The differential diagnosis from infectious mononucleosis (glandular fever) may turn on the Paul-Bunnell reaction—not an entirely reliable sign—but the blood picture in infectious lymphocytosis shows only small lymphocytes, with no glandular fever cells or excess of monocytes. In lymphatic leukemia the patient is much more ill and has a rapidly increasing anemia, and sternal puncture always shows a massive lymphocytic infiltration.

The prognosis in infectious lymphocytosis is excellent, even if the course is long; no specific treatment has been proposed. The cause has not been identified; it has, as usual, been ascribed to a virus, but no supporting evidence has appeared yet.

The Lancet, Vol. 251, P. 949

FOLIC ACID

THE INTRODUCTION of folic acid constitutes one of the most important therapeutic advances of the past year. This substance is the latest addition to the growing family of the vitamin B-complex group and, because of the many conditions in which it has already been found to be of value, it seems probable that it may become more widely used than any of its close relatives.

Indications—It has been shown that folic acid is very closely allied to, if not identical with, the red cell maturation factor long known to have been present in liver extract and yeast. It has been found to be highly effective when given either orally or parenterally in inducing remissions in sprue, celiac disease, pernicious anemia and other macrocytic anemias.

Whether or not folic acid will supplant liver extract as the primary therapeutic weapon in pernicious anemia is not known. It has been found that remissions which are characterized by a reticulocyte response and an increase in red and white blood counts, platelets, and hematocrit values occur regularly following the daily oral administration of a few milligrams of folic acid to patients with pernicious anemia in relapse. Whether or not complete remissions can be maintained indefinitely by continuing this therapy or whether or not the neurological disturbances often associated with pernicious anemia can be satisfactorily controlled by folic acid therapy awaits further study. For the present it seems best to combine parenteral liver extract with folic acid therapy in all cases of pernicious anemia associated with postero-lateral sclerosis.

In sprue and celiac disease the daily oral or parenteral administration of folic acid is attended by a rapid improvement in appetite, by a decrease in the number and bulk of the stools, and by a return of the blood picture to normal. The results are superior to those obtained by the use of liver extracts and special diets. It is important, however, that an adequate diet be given. Small doses of folic acid given daily probably are necessary to prevent recurrences in these patients.

In the macrocytic anemias associated with nutritional diseases (pellagra), pregnancy, liver disease (cirrhosis) and those which may follow gastric resection, folic acid has been shown to be highly effective, the results being better than those following liver extract therapy. Best results are obtained when the drug is given intravenously.

Dosage—The final word on ideal dosage of folic acid cannot be stated at this time. In treating pernicious anemia, 10 to 20 mg. given daily in divided doses by mouth seem sufficient to induce remissions in nearly all cases. Following return of the blood to normal, 5 mg. daily is probably a large enough dose to prevent relapse. Similar doses are indicated in sprue and celiac disease. When parenteral therapy is indicated, 1-5 mg. are given intravenously or intramuscularly once or twice daily.

Toxic effects—Unpleasant side effects are encountered rarely when the doses mentioned are given. Gastrointestinal upsets may occur, but are usually controlled by a reduction in dosage. When the drug is given intravenously the usual precautions of such procedures must be observed.

Bulletin of the New England Medical Center, Vol. 3, P. 274.

New Drugs

The information in this department has been supplied to Postgraduate Medicine by the manufacturers of the products described.

GELFOAM, NO. 12, STERILE

PURPOSE: To provide hemostasis in neurosurgery, otolaryngology, bone surgery, malignancy, abdominal surgery, and proctology.

DESCRIPTION: Gelfoam is prepared from a non-antigenic, specially treated gelatin solution which is processed to give the desired porosity, dried, sectioned and sterilized.

INDICATIONS FOR USE: Soak gelfoam in sterile saline or thrombin solution and apply to bleeding area. Gelfoam is completely absorbed in about four weeks when implanted in tissues and does not cause excessive scar tissue formation.

HOW SUPPLIED: In jars containing four sterile sponges each having a surface area of 12 square centimeters.

PRODUCER: The Upjohn Company, Kalamazoo, Mich.

OENETHYL HYDROCHLORIDE

PURPOSE: Vasopressor substance for spinal anesthesia.

COMPOSITION: 2-methylaminoheptane.

DESCRIPTION: An aliphatic amine. A colorless, volatile fluid, slightly soluble in water which combines with acids to form salts which are readily soluble in water.

INDICATIONS FOR USE: Oenethyl hydrochloride is a vasoconstrictor having a pressor effect indicated in spinal anesthesia to raise a depressed blood pressure. Therapeutic doses of Oenethyl rarely cause undesirable side effects, such as nervousness, palpitation, headache, and dizziness. Oenethyl is indicated only in combatting hypotension brought about by spinal anesthetic.

DOSAGE: Intravenously or intramuscularly in doses of 1 cc. (50 mg.) divided in doses of 5 to 10 mg. (0.1 cc. to 0.2 cc.) at 15- to 30-second intervals with continuous check on changes in blood pressure. Whether intravenous or intramuscular route is used is dependent upon the depth of fall of the blood pressure and urgency of the case.

HOW SUPPLIED: Ampules of 1 cc. each containing 50 mg. (¾ grain) 2-methylaminoheptane hydrochloride in boxes of 6 and 100.

PRODUCER: Bilhuber-Knoll Corp., Orange, N. J.

ALCO-DEX

PURPOSE: A substitute for morphine in the relief of post-operative pain.

COMPOSITION:

Alcohol	5 per cent
Dextrose in saline with Vitadex	5 per cent
Thiamin chloride	3 mg.
Riboflavin	4.5 mg.
Nicotinamide	30 mg.
Pyroxidine hydrochloride	3 mg.

DESCRIPTION: An intravenous solution which relieves postoperative pain and supplies food, salt, and fluids to the patient's system. The action of Alco-Dex is slower than morphine, but it is non-habit forming and does not cause constipation or postoperative distention. The alcohol tends to increase the respiratory rate and in this way has a protective action against pulmonary complications which may follow surgery. Alco-Dex is a source of calories and contains sufficient amounts of B-complex to counteract the deficiency of those vitamins caused by carbohydrates and alcohol.

INDICATIONS FOR USE: As soon as the postoperative patient feels any pain.

DOSAGE: Suggested rate of administration would be 50-70 drops per minute, approximately 200-250 cc. of 5 per cent solution per hour, depending upon the tolerance of the patient.

CAUTIONS: Because the action of alcohol as an analgesic is slower than morphine, even though more prolonged, it is suggested that medication be started as soon as the patient feels any pain rather than waiting until pain is acute as sometimes is done in the use of morphine.

HOW SUPPLIED: Available in four different combinations in liter flasks.

PRICE:

	1-7 Cases	8 Cases or More
Alcohol 5% with Vitadex B in D-5-S	1.65	1.50
Alcohol 10% with Vitadex B in D-5-S	2.20	2.05
Alcohol 5% with Vitadex B in D-5-W	1.60	1.45
Alcohol 10% with Vitadex B in D-5-W	2.15	2.00

PRODUCERS: Cutter Laboratories, Berkeley, Cal.

After Office Hours

We have been impressed by the appeal of a large insurance company for everyone to engage in a hobby—any hobby. This organization says that having a hobby will add years to a person's life and we are of the same opinion.

We have heard doctors say that all men, especially in the medical profession, need subordinate avocations. John Fallon, surgeon of Worcester, Massachusetts, has occupied his spare moments by collecting Medica Litteraria—poems, novels, philosophies, plays, and essays. His collection may be favorably compared to those of Mayo, Holmes, Osler, or Cushing. His home is a storehouse of medical incunabula.

We cornered Doctor Fallon at a recent American College of Surgeons meeting and asked him to tell us more about his hobby. Being something of a poet himself, he talked about doctors and poetry. "Some doctors have put out their verse from behind false mustaches or pseudonyms, perhaps because of the opinion that poets are irresponsible fellows. If you had, say pneumonia, and suddenly found that your doctor, that strong quiet man between you and death, was writing an 'Ode to a Robin,' wouldn't your confidence go down and your temperature go up?

"Yet," continued Doctor Fallon, warming up to his favorite topic, "there is a fundamental kinship between the doctor and the poet. True, medicine is keeping calm, knowing booksful of facts and figures, listening patiently, deciding coldly and poetry is sky-rockets and explosions. Medicine is snuffy noses and lumbago; poetry is visions. But medicine is essentially sympathy, the desire to help a fellow man in sorrow, need and sickness. And so is poetry. The poet is the doctor of the sick soul: he makes them believe, and hope, and go on. And there are two other bonds between the doctor and the poet: both of them neglect their families for their work and forget their fees."

* * *

One doctor who was past seventy when someone suggested book-collecting to him, stated that this interest had added ten years to his life by providing zest to his days.

* * *

Music offers one of the finest means of relaxing and the best musical relaxation of all is to *make* music, not listen to it; to sing in a chorus or to play something, preferably with a group. Action, self controlled, a psychologist will tell you, is the solution for all kinds of fears and tensions.

Doctors who wouldn't live in New York if we gave them the place are seriously advised to reconsider their pronunciamento. They would have difficulty recognizing the town around Irving Place at Eighteenth Street. While keen-eared observers probably suspect the worst, weekly rehearsals of the Doctors' Orchestral Society of New York are held every Thursday at the National Hospital for Speech Disorders.

According to reports in a recent *New Yorker,* the orchestral society has been active since 1938 and includes several dozen medical men about town. Of a Thursday night one is apt to see and hear Dr. William Spielberg, a nose-and-throat and violin specialist; Dr. Charles Auer, internist-flutist; Dr. Sidney Robbins, dermatologist-violinist; Dr. Charles Gottlieb, x-rays and viola; Dr. Ricardo Gorbea, obstetrics and oboe; Dr. Abe Salzman, pathology and bass fiddle; Dr. Charles Gardner, dentist-violist, and Dr. Alexander Sved, orthodontist-violist. The president of the society is Dr. Cornelius H. Traeger, a diagnostician who specializes in arthritis and the bass fiddle. With the income from annual dues of $25.00, the society has bought an extensive library of arrangements and pays for the services of a non-medical conductor.

For public performances, the orchestra is augmented by a few non-medicos, and even at rehearsals a handful of ringers play—a second-violin lawyer for instance, who takes care of the society's few legal matters. Because of the unpredictable nature of their profession the doctors do not know what kind of an orchestra may be assembled on any particular night. One Thursday, six clarinettists and only two cellists will show up; the following week there'll be two clarinettists and eight cellists. The society is looking for

a harpist and could use two French horns, an English horn, and a bass trombone.

* * *

One doctor we know whose hobby is collecting old insurance blanks which are found among reports to the British and American medical journals, has a lot of fun with a collection such as the following:

Mother died in infancy.

Father went to bed feeling well and next morning woke up dead.

Applicant has never had a fatal illness.

Grandfather died from gunshot wound caused by an arrow shot by an Indian.

Father died, suddenly—nothing serious.

Mother's last illness was chronic rheumatism but she was cured before she died.

* * *

Dr. Carl Binger of Cornell University Medical College has charged that the incessant "hammering" of radio commercial plugs to make listeners brand-conscious" has become a serious source of medical misinformation. Dr. Binger also lashed out against Hollywood's pseudo-psychiatric motion pictures.

The doctor who, say, has sixteen years of medical education with ten years of specialization in psychotherapy, is caught flat-footed because he can not understand the vernacular his patients have acquired from the movies. Gordon Kahn, Hollywood specialist on the subject, suggests that the following might happen to any old fashioned doctor who has not kept up with movie versions of psychiatric methods:

"Ah, dreams," probes the doctor.

"And the only way I can describe them is in simple layman's language. They're anagogic. Anagogic as all get out."

The doctor defrosts. He thinks here is a simple fellow who has picked up a few random professional phrases while shopping around for treatment. And now, By Messmer!—he'll get it. "I might suggest a trial analysis."

"Where have you been, Doc? Why that technique went out with 'Lady in the Dark'—you know where Ginger Rogers goes off into a lot of yackeytyack there on the couch."

"Just to fix a point of departure."

"Frame of reference, you mean."

"Precisely, by free association—"

"Are you kidding, Doc? That stuff was all right in 'Spellbound,' where Bergman and that little Russian analyst had Gregory Peck on the ropes. Put old Freud back on the shelf along with Charcot."

"But Freud discovered—"

"And so did Columbus. But you wouldn't think of using his maps now! What about Selznick and Zanuck—" The patient himself is a busy man. He wants to catch "The Spiral Staircase" and "The Blue Dahlia" before the night prices go on.

"I'll go in for narcosis," he says, "the way Doc Larsen gave it to Ann Todd in 'The Seventh Veil.' Just hit me lightly with one cubic centimeter of pentothal intramuscularly, and in a couple of minutes I'll open up like fourth-class mail."

And no reaching for that crock of insulin, either, Doc. This man is hep. He's seen the movie "Shock." Twice he's seen it! He knows what a psychiatrist is likely to do with a hypo of insulin.

* * *

A letter from Charles Brown of San Antonio, Texas, gives us the news that the Naylor Company of that city is about to publish his book, *Bars from Bilibid Prison*. Doctor Brown, who has had thirteen years of active service in the Army Medical Corps, tells us that this collection of more than one hundred poems was written during his three years' captivity in Bilibid prison following the fall of Bataan. The poems are printed as they were originally written on scraps of paper and not a line or a word has been changed. Here is the philosophy of a prisoner—of all prisoners—of all times.

Doctor Brown says: "If you will bear with me, I would like to tell you a little about it. I have arranged the poems in four sections with an explanatory text that is an attempt on my part to tell briefly: (1) the history of the Spanish prison Bilibid, (2) the siege of Bataan and Corregidor, (3) the events of our three years as prisoners and the story of medical work done there, (4) the liberation of the prison. Interspersed are the 'Bars,' or poems. Some of them are in a serious vein, while others are for the most part, of a humorous nature."

Doctor Brown was born in Tennessee and has lived most of his life in Texas. At present, as Major Brown, he is surgeon for the Army Medical School, recently moved to San Antonio from Carlysle Barracks, Pennsylvania. He is married and has a young daughter who thinks he writes "funny things." Doctor Brown adds a postscript in his letter to us: "I must tell you this: while I was a prisoner I was allowed to send a postcard to my wife after the first two years. Inasmuch as Francis Ticknor's little poem had always been a favorite of ours since childhood, I signed the card 'Little Giffen'—it told her more about my situation than a dozen pages, as you can well appreciate!"

M. L. Mc D.